Pharmacology & Therapeutics 202 (2019) 18–31

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Vascular Disrupting Agents in cancer treatment: Cardiovascular toxicity and implications for co-administration with other cancer chemotherapeutics

Jason H. Gill [a,b,*], Kimberly L. Rockley [a], Carol De Santis [a], Asma K. Mohamed [a]

[a] Northern Institute for Cancer Research (NICR), Faculty of Medical Sciences, Newcastle University, UK
[b] School of Pharmacy, Faculty of Medical Sciences, Newcastle University, UK

ARTICLE INFO

Available online 5 June 2019

Keywords:
Cancer therapy
Cardiovascular toxicity
Cardioncology
Vascular disrupting agents

ABSTRACT

Destruction of the established tumour vasculature by a class of compound termed Vascular Disrupting Agents (VDAs) is showing considerable promise as a viable approach for the management of solid tumours. VDAs induce a rapid shutdown and collapse of tumour blood vessels, leading to ischaemia and consequent necrosis of the tumour mass. Their efficacy is hindered by the persistence of a viable rim of tumour cells, supported by the peripheral normal vasculature, necessitating their co-administration with additional chemotherapeutics for maximal therapeutic benefit. However, a major limitation for the use of many cancer therapeutics is the development of life-threatening cardiovascular toxicities, with significant consequences for treatment response and the patient's quality of life. The aim of this review is to outline VDAs as a cancer therapeutic approach and define the mechanistic basis of cardiovascular toxicities of current chemotherapeutics, with the overall objective of discussing whether VDA combinations with specific chemotherapeutic classes would be good or bad in terms of cardiovascular toxicity.

Contents

Abbreviations: AML, Acute myeloid leukaemia; CA4P, Combretastatin-A4-phosphate; CA4DP, Combretastatin-A4-disodium-phosphate; CLL, Chronic lymphocytic leukaemia; ECG, Electrocardiogram; 5-FU, 5-Fluorouracil; GI-NET, Gastrointestinal neuroendocrine tumour; MMC, Mitomycin C; mTOP, Mitochondrial topoisomerase; NSCLC, Non-small cell lung cancer; PNET, Primitive neuroectodermal tumour; QTc, Corrected Q-T interval measured by electrocardiogram; SCLC, Small cell lung cancer; TOPI, Topoisomerase type 1; TOPII, Topoisomerase type 2; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; VDA, Vascular disrupting agent.

* Corresponding author at: Northern Institute for Cancer Research (NICR), Paul O'Gorman Building, Medical School, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.
E-mail address: jason.gill@newcastle.ac.uk (J.H. Gill).

https://doi.org/10.1016/j.pharmthera.2019.06.001
0163-7258/

1. Introduction

Increased understanding of the molecular basis of cancer over the past decade has advanced cancer chemotherapy into an era of "targeted molecular therapeutics" alongside "conventional cytotoxic agents" (Collins & Workman, 2006; Weinstein & Joe, 2006). However, despite many of these medicines significantly improving cancer treatment and patient survival, it is now clear that their benefit is counterbalanced by adverse toxic effects, particularly upon the cardiovascular system (Alameddine et al., 2015; Dy & Adjei, 2013; Raschi et al., 2010; Tocchetti et al., 2013). Consequently, challenges exist with respect to identifying, managing or at least monitoring cancer-therapy related cardiovascular toxicity, to provide the most beneficial cancer treatment, ultimately improving patient outcomes and longer-term healthcare. A task and activity which led to the emergence of cardioncology as a defined discipline (Ky, Vejpongsa, Yeh, Force, & Moslehi, 2013; Todaro et al., 2013). In order to administer safer yet still effective cancer treatments, a much greater appreciation of the underlying molecular mechanisms by which current therapies cause adverse effects upon the cardiovascular system and how to predict these toxicities before they arise in the clinic is essential.

In terms of clinical presentation, chemotherapy-induced cardiotoxicity is classified into three types: symptomatic acute toxicity occurring soon after administration, and early- and late-onset chronic toxicity, occurring before or after one year of treatment, respectively (Bagnes, Panchuk, & Recondo, 2010; Curigliano, Mayer, Burstein, Winer, & Goldhirsch, 2010; Yeh, 2006). Due to the often asymptomatic nature of acute cardiotoxicity, which presents as rhythm disturbances, transient reductions in myocardial contractility, and/or hypotension, and the fact that it is reversible by discontinuation of treatment, this adverse effect is commonly under recognised. The infrequency of this cardiotoxicity subtype does not equate to it being inconsequential or irrelevant; as sub-clinical adverse effects may contribute to cumulative cardiac damage or asymptomatic loss of cardiac function. In the case of early- and late-onset chronic progressive cardiotoxicities, these are associated with electrophysiological changes and left ventricular dysfunction, which presents clinically as irreversible cardiomyopathy (Curigliano et al., 2012). With late-onset chronic progressive cardiotoxicity, the deterioration in cardiac function is progressive over many years and can be as long as one to two decades after completion of cancer therapy.

Chemotherapy-induced toxicity, although commonly manifesting as an effect upon the cardiac system, also poses a risk to the coronary and peripheral vascular systems, through exacerbation of hypertension, perturbations in vascular tone, or direct vascular damage (Herrmann et al., 2016). Alongside cardiac toxicity, this obviously has an effect upon the circulatory cardiovascular system and indirectly upon the heart itself. Several chemotherapeutic drugs, most notably the molecular targeted kinase inhibitors, have been shown to induce vascular toxicity in the clinic (Herrmann et al., 2016; Touyz, Herrmann, & Herrmann, 2018). However, unlike the recent cross-disciplinary awareness of chemotherapy-induced cardiotoxicity, vascular toxicity per se is still largely under-appreciated in the clinic and strategies targeted towards its mitigation and management are not fully defined. Nevertheless, chemotherapy-induced effects upon the vascular system remain important and directly pertinent to cancer management and cardioncology.

Cardiovascular toxicity is without doubt a long-term complicating factor in cancer treatment, from asymptomatic electrocardiographic perturbations through to symptomatic life-threatening events such as heart failure, appearing both acutely and taking several years to manifest (Cardinale, Biasillo, & Cipolla, 2016; Salvatorelli et al., 2015; Todaro et al., 2013). Despite this, the severity and life-threatening nature of cancer in conjunction with the improvement in overall survival associated with treatment often outweighs these toxicological safety risks (Salvatorelli et al., 2015; Todaro et al., 2013).

2. Tumour vasculature as a therapeutic target in cancer

Tumour growth and expansion, invasive capacity and ultimately metastasis and dissemination to other parts of the body, are all hugely dependent upon a functioning vascular network (Tozer, Kanthou, & Baguley, 2005; Weis & Cheresh, 2011). The absence or failure of a tumour to sustain a viable blood flow causes a restriction in growth and cessation of progression due to lack of nutrition and oxygen, and build-up of metabolic waste products and carbon dioxide (Tozer et al., 2005). Similarly, the inability or prevention of a tumour to develop new blood and lymphatic vessels (angiogenesis and lymphangiogenesis) causes a restriction in growth volume to a few millimetres and concomitant tumour dormancy (Weis & Cheresh, 2011). Consequently, targeting of the vasculature within tumours has significant potential for therapeutic intervention (Ji, Liu, & Liu, 2015; Tozer et al., 2005; Weis & Cheresh, 2011), with strategies broadly categorised into two areas; i) inhibition or interference in the development and recruitment of a new vascular supply to the tumour with consequent stasis of tumour expansion, through perturbation of the angiogenic process (Weis & Cheresh, 2011), and ii) disruption and collapse of the existing tumour vasculature, resulting in 'tumour starvation', and consequent tumour necrosis and death (Ji et al., 2015; Tozer et al., 2005) (see Fig. 1).

The former of these areas, the anti-angiogenesis therapeutic strategy, has seen an explosion of interest over the past 'molecular therapeutic' decade and has resulted in advancement of agents in this class into the clinic with significant success (Shahi & Pineda, 2008; Weis & Cheresh, 2011). The majority of these anti-angiogenic therapeutics are concerned with blockade of vascular endothelial growth factor (VEGF) activity within the tumour, through either sequestering circulating VEGF, blockade of the VEGF-receptor, or disruption of the intracellular signalling pathway (Weis & Cheresh, 2011). It is now clearly evident that these anti-angiogenic therapies exhibit a significant adverse effect upon the cardiovascular system, particularly hypertension and heart failure (Alameddine et al., 2015; Cameron, Touyz, & Lang, 2016; Ky et al., 2013; Tocchetti et al., 2013; Vasiliadis, Kolovou, & Mikhailidis, 2014). This is briefly discussed later in this review.

In contrast to anti-angiogenic approaches which prevent neovasculature development, the vascular-disrupting strategy for cancer treatment is focused on affecting the 'established' vasculature within the tumour (see Fig. 1). In 'normal' non-tumorous tissue, the vasculature architecture is organised into regular structures, with mature endothelial cells forming a defined lumen supported by a well-established network of pericytes and smooth muscle cells (Baluk, Hashizume, & McDonald, 2005; Barlow, Sanders, Soker, Ergun, & Metheny-Barlow, 2013; Siemann, Chaplin, & Horsman, 2017; van Dijk et al., 2015). In contrast, as a consequence of the rapid and relatively uncoordinated nature of their development, tumour vascular networks are particularly unorganised and formless, with random irrational vessel connections and chaotic blood flow (Baluk et al., 2005; Barlow et al., 2013; Siemann et al., 2017). Furthermore, tumour vasculature is actively growing and lacks control mechanisms that are protective to blood flow normalcy (Baluk et al., 2005; Barlow et al., 2013; Deryugina & Quigley, 2015). The differential in vasculature structure and blood flow across the tumour, the rapid growth and concomitant dependency on a supportive blood supply, and the immaturity of the endothelial cells within the tumour therefore exposes the validity of targeting vascular supply to limit and inhibit tumour growth, survival, and dissemination. Consequently, selectively disrupting the established blood supply to tumours is now known to be an effective therapeutic strategy, with several vascular disrupting agents (VDAs) targeting the colchicine-binding domain of β-tubulin currently in preclinical development or late stage clinical trial (Ji et al., 2015; Mason, Zhao, Liu, Trawick, & Pinney, 2011), as shown in Table 1. The underlying mechanism as to why these agents have such a profound effect on tumour over "normal" blood vessels has yet to be conclusively proven clinically. However, there is compelling preclinical information to suggest that the demands of the tumour and its

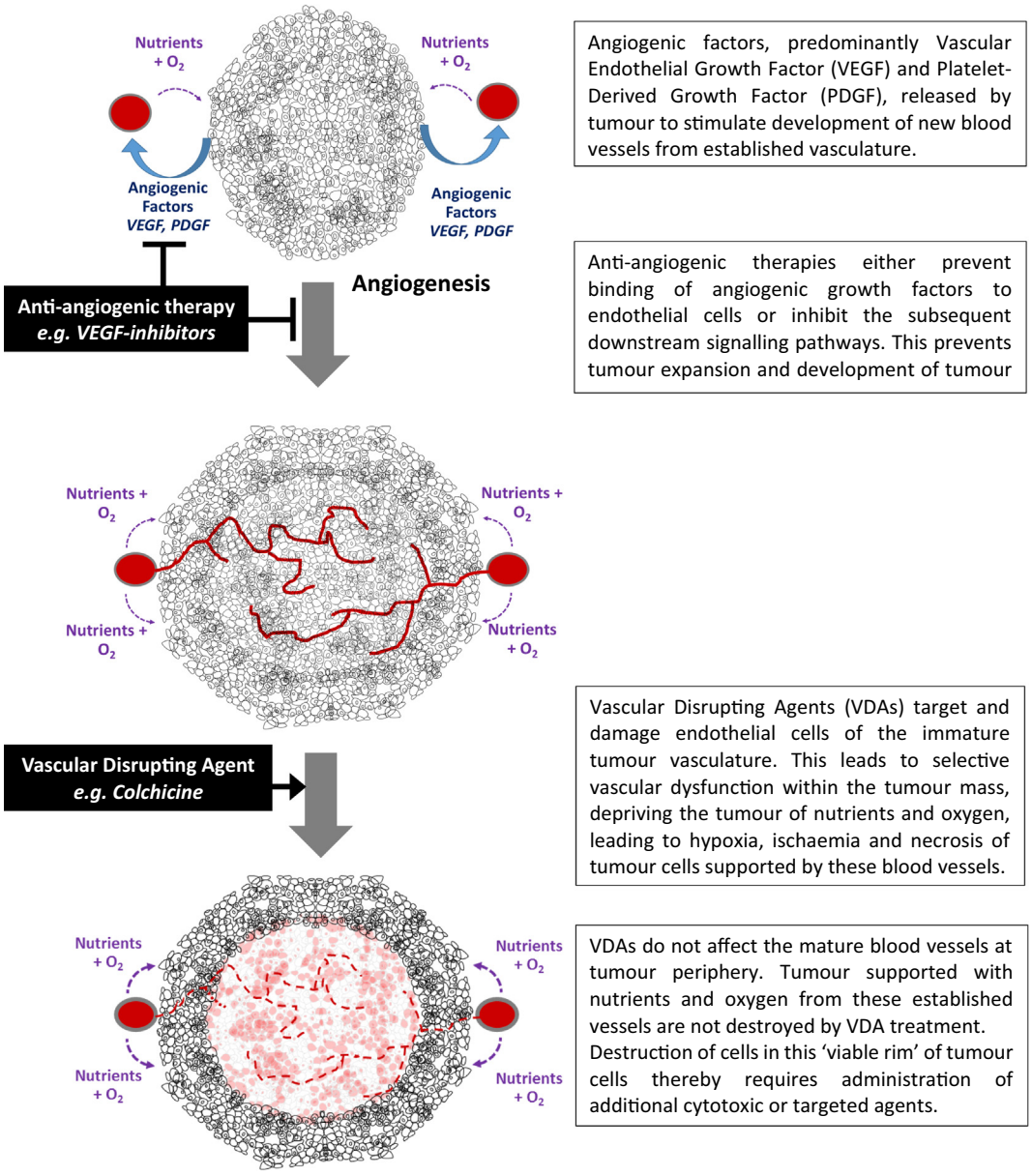

Fig. 1. Mechanism of agents targeting tumour vasculature as a therapeutic approach in cancer: Vascular disrupting agents (VDA) and anti-angiogenic therapies.

environment presents the tumour endothelial cells with an abnormal cellular physiology, such that their immaturity results in their rigidity and shape being dependent upon an intracellular tubulin cytoskeleton rather than the largely actin cytoskeleton present in mature established endothelial cells and blood vessels (Furst & Vollmar, 2013; Kanthou & Tozer, 2009; S. Kim, Peshkin, & Mitchison, 2012; Mahal, Biersack, Caysa, Schobert, & Mueller, 2015; Schwartz, 2009). Consequently, agents which disrupt tubulin dynamics would have a profound effect on tumour endothelial cell structure, with minimal effects to endothelial cells in mature blood vessels. Furthermore, it is now well established that the disruption of a single tumour blood vessel results in death of the large number of tumour cells it supports (Kanthou & Tozer, 2007; Mita, Sargsyan, Mita, & Spear, 2013; Tozer et al., 2005). Additionally, the destabilization of the tumour endothelium leads to a temporal enhancement of vascular permeability and consequent drug retention, with significant potential for therapeutic enhancement (Mason et al., 2011; Reyes-Aldasoro et al., 2008; Tozer et al., 2005).

VDAs offer several positive therapeutic attributes relative to the majority of cancer therapeutics. Firstly, they are not required to extravasate from the blood vessel and penetrate across several cell layers for their activity and thus are not hindered by intra-tumoural pharmacokinetic dilution. Secondly, they target a fundamental process for survival of all solid tumours and therefore have widespread potential, through affecting 'non-tumorigenic cells' within the tumour microenvironment avoiding undesirable acquired drug resistance associated with genomic instability of malignant cells (Kanthou & Tozer, 2007; Lippert III, 2007; Mita et al., 2013). Despite exhibiting significant potential, it is becoming increasingly apparent that the therapeutic value for these colchicine-related VDAs is compromised by their intrinsic toxicity, including cardiac toxicities (Chase et al., 2017; Hinnen & Eskens, 2007; Ho, Wang, Fan, & Yeh, 2017; Mita et al., 2013; Siemann, Chaplin, & Walicke, 2009; Subbiah, Lenihan, & Tsimberidou, 2011)

2.1. Cardiotoxicity of vascular disrupting agents

Several preclinical *in vivo* laboratory investigations and clinical trials have been performed to evaluate toxicity of the tubulin-interactive VDAs (Beerepoot et al., 2006; Hinnen & Eskens, 2007; Ho et al., 2017;

Table 1
Tubulin-targeted VDAs in clinical development

VDA	Company	Stage of development	Combination therapies	References
ABT-751[a]	Abbvie	Phase II (Multiple cancer types)	Pemetrexed (NSCLC); Carboplatin (NSCLC); Docetaxel (Prostate cancer)	(Fox et al., 2008; Hande et al., 2006; Ma et al., 2012; Mauer et al., 2008; Michels et al., 2010; Rudek et al., 2016; Rudin et al., 2011; Yee et al., 2005)
BNC105 / BNC105P	Bionomics	Phase I (Multiple cancer types); Phase I (CLL); Phase II (Renal & colorectal cancers); Phase II (Mesothelioma)	Everolimus (Renal Cancer); Carboplatin & gemcitabine (Ovarian cancer); Ibrutinib (CLL); Nivolumab (Colorectal cancer)	(Lindemann et al., 2019; Nowak et al., 2013; Pal et al., 2015; Rischin et al., 2011)
CKD-516 (NOV120401)	Chong Kun Dang Pharmaceutical	Phase I (Multiple cancer types); Phase I/II (Colorectal cancer)	Irinotecan (Colorectal cancer)	(Oh et al., 2016)
Crolibulin (EPC2407)	Cytovia / Immune Pharmaceuticals	Phase II (Thyroid cancer)	Cisplatin (Thyroid cancer)	(Gramza, Balasubramaniam, Fojo, Ward, & Wells, 2013)
Denibulin (MN-029)	Medicinova	Phase I (Multiple cancer types)	None reported to date	(Ricart et al., 2011; Traynor et al., 2010)
Fosbretabulin (CA4P)	Mateon Therapeutics (Oxigene)	Phase I (Multiple cancer types); Phase III (Ovarian cancer); Phase II (Glioblastoma); Phase II (Thyroid cancer); Phase II (GI-NETs/PNETs); Phase II (Melanoma)	Carboplatin & paclitaxel (Ovarian cancer); Bevacizumab (Ovarian cancer); Pazopanib (Ovarian cancer); Carboplatin, paclitaxel, & bevacizumab (NSCLC); Carboplatin & paclitaxel (Thyroid cancer); Everolimus (PNETS); Nivolumab (Melanoma)	(Chase, Chaplin, & Monk, 2017; Chauhan et al., 2018; Chauhan, Arnold, Dressler, Nichols, & Anthony, 2018; Cooney et al., 2004; Garon et al., 2016; Grisham, Ky, Tewari, Chaplin, & Walker, 2018; He et al., 2011; Libutti, Anthony, Chaplin, & Sosa, 2017; Liu et al., 2014; Rustin et al., 2003; Sosa et al., 2011; Zweifel et al., 2011)
Lexibulin (CYT997)	Cytopia / YM Biosciences /Gilead Sciences	Phase I (Multiple cancer types); Phase Ib (Glioblastoma); Phase II (Multiple myeloma)	Carboplatin (Glioblastoma)	(Burge et al., 2013; Lickliter et al., 2008; Lickliter et al., 2010)
Ombrabulin (AVE8062)[a]	Sanofi-Aventis	Phase I (Multiple cancer types); Phase II (NSCLC); Phase III (Sarcoma)	Taxane/Platinum (Multiple solid cancer types); Cisplatin (Multiple solid cancers); Docetaxel (Multiple solid cancers); Bevacizumab (Multiple solid cancers)	(Bahleda et al., 2014; Blay et al., 2015; Conte et al., 2012; Eskens et al., 2014; Murakami et al., 2014; Nishio et al., 2018; Sessa et al., 2013; von Pawel et al., 2014)
Oxi4503 (CA41P)	Mateon Therapeutics (Oxigene)	Phase I (Multiple cancer types); Phase II (Hepatic tumours); Phase II (Acute myeloid leukaemia)	Cytarabine (Acute myeloid leukaemia)	(Cogle et al., 2012; Mainwaring et al., 2010; Patterson et al., 2007; Patterson et al., 2012; Turner et al., 2013; Watts, Swords, Cogle, Schiller, & Lin, 2017)
Plinabulin (NPI-2358)	BeyondSpring Pharmaceuticals	Phase I/II (Multiple cancer types); Phase II (NSCLC); Phase II (SCLC)	Docetaxel (NSCLC); Nivolumab (Melanoma) Nivolumab & ipilimumab (SCLC)	(Heist et al., 2014; P. LoRusso et al., 2007; Millward et al., 2012; Millward et al., 2009; Mita et al., 2010)
Soblidotin (TZT-1027)	Daiichi Sankyo	Phase I (Multiple cancer types); Phase II (Sarcoma); Phase II (NSCLC)	Carboplatin (Multiple solid cancers)	(de Jonge et al., 2005; Greystoke et al., 2006; Horti et al., 2008; Patel et al., 2006; Riely et al., 2007; Tamura et al., 2007; Yamamoto, Andoh, Kawahara, Fukuoka, & Niitani, 2009)
Verubulin (MPC-6827)	Myrexis / Cytovia	Phase I (Multiple cancer types); Phase I/II (Glioblastoma)	Carboplatin (Glioblastoma) Temozolamide (Glioblastoma)	(Chamberlain et al., 2014; Grossmann et al., 2012; L. J. Kim et al., 2011; Zhu et al., 2011)
ZD6126[a]	Angiogene Pharmaceuticals	Phase II (Multiple cancer types)	Oxaliplatin & 5-Fluorouracil (Colorectal Cancer)	(Beerepoot et al., 2006; P. M. LoRusso et al., 2008)

[a] Development discontinued

Sessa et al., 2013; Subbiah et al., 2011; Tozer et al., 2005). In several cases VDAs have been shown to cause a wide range of detrimental effects upon the cardiovascular system (Table 2) (Hinnen & Eskens, 2007; Ho et al., 2017; Siemann et al., 2009; Subbiah et al., 2011).

Preclinical studies of cardiac effects of the tubulin-binding VDAs, ZD6126 and the combretastatin family of anticancer drug, were performed in rats, involving continuous monitoring of both heart rate and blood pressure alongside histopathological and biochemical analyses (Anderson et al., 2003; Gould et al., 2007; Grosios, Holwell, McGown, Pettit, & Bibby, 1999; Jaroch et al., 2016; P. M. LoRusso et al., 2008; Rustin et al., 2010; Subbiah et al., 2011; Tochinai et al., 2016; Zweifel et al., 2011). Administration of ZD6126 was associated with high levels of circulating troponin T (clinical biomarker of cardiac toxicity) in the blood and drug-induced delayed tachycardia and hypertension (Gould et al., 2007). In the case of combretastatin-A4-phosphate (CA4P) and its analogue combretastatin-A4-disodium-phosphate (CA4DP), drug-induced increases in mean arterial blood pressure were also observed. However, no detectable increases in troponin were observed (Ke et al., 2009). Interestingly, pre-administration of calcium channel blockers prevented hypertension induced by both ZD6126 and combretastatins in these rat models (Gould et al., 2007; Ke, Samad, Bae, Chaplin, & Kang, 2015), offering the notion that VDA-related elevated blood

Table 2
VDA-induced cardiac effects reported in preclinical and clinic studies

VDA-induced cardiac ischaemia
Myocardial infarction
Asymptomatic elevation in circulating troponin I levels
VDA-induced haemodynamic changes
Hypertension
Hypotension
VDA-induced perturbations in cardiac electrophysiology
Transient QT prolongation
Delayed ventricular repolarisation
Tachycardia
Bradycardia
Atrial fibrillation

pressures maybe linked to increased peripheral vessel resistance (Anderson et al., 2003; Grisham et al., 2018).

In clinical trials, several cardiotoxic effects were detected within a few hours of administration of ZD6126, including abnormal cardiac function, pain or pressure in the mid-chest region or left arm, and increased systemic levels of the biomarker of cardiotoxicity troponin (Beerepoot et al., 2006). Although CA4P is tolerated better than ZD6126 and other VDAs, its use is still accompanied by a range of cardiac adverse effects. The most common adverse effect of CA4P is an acute transient increase in baseline blood pressure, wherein a 10-15% increase above baseline is observed within one hour of administration, with normal state returning within 3-4 hours post-infusion (Grisham et al., 2018). Drug-induced tachycardia and contradictory bradycardia are both evident with CA4P therapy; typically characterised by a decrease in heart rate (bradycardia) within the first hour post-infusion followed by an increase (tachycardia) around 3-4 hours later, and a return to baseline by 24 hours (Grisham et al., 2018; Rustin et al., 2003; Zweifel et al., 2011). Several patients receiving CA4P have also experienced myocardial ischaemia, although in the majority of cases an underlying confounding issue was identified, such as coronary artery disease (Garon et al., 2016; Grisham et al., 2018; Rustin et al., 2003; Sosa et al., 2014).

In terms of clinical management of CA4P-induced cardiac effects, a treatment algorithm was devised for use in the phase II FOCUS trial (CA4P in combination with the anti-angiogenic agent bevacizumab and cytotoxic chemotherapy) involving differential strategies for patients presenting with hypertension and those normotensive (Monk et al., 2016). Patients with hypertension were managed through optimisation of their current medication, and in those patients without established hypertension an evaluation of cardiovascular risk factors was undertaken prior to receiving CA4P (Grisham et al., 2018; Monk et al., 2016). High-risk patients were those with any previous CA4P-induced blood pressure effect or with baseline blood pressure >130 mmHg, and the presence of cardiovascular risk factors (diabetes, previous myocardial infarction, prior uncontrolled hypertension etc.). A major risk factor of pertinence for cancer therapy was also receipt of prior anthracyclines, an issue which will be appraised later in this review. However, in all cases, frequent monitoring of blood pressure after CA4P administration was deemed essential to mitigate the acute CA4P-induced cardiac complications (Grisham et al., 2018; Monk et al., 2016).

2.2. Necessity for use of VDAs in combination therapy

Despite showing significant potential as a potent therapeutic strategy for the management of many solid cancers, the major limitation of VDAs are their inability to significantly affect those cells at the periphery of the tumour mass, in the so-called "viable tumour rim" (see Fig. 1). (Blakey, Ashton, Westwood, Walker, & Ryan, 2002; Tozer et al., 2005). As such, the endothelial cells of these established blood vessels no longer rely on the tubulin cytoskeleton for their structure, but rather a more well-established cytoskeletal structure underpinned by actin and other such fibres, with consequences for the success of VDAs (Tozer et al., 2005). Furthermore, blood vessels located within the tumour periphery are associated with a high density of supporting pericytes, known to play an important role in microvascular stabilisation and hypothesised to contribute to the resistance to VDAs in this region (Chen et al., 2017; Tozer et al., 2008).

Consequently, clinical administration of a VDA will need to be accompanied with a therapeutic to effectively target these persistent cells, most notably a cytotoxic therapeutic (Table 1). In contrast to this being perceived negatively, the reality is actually the converse with the two-pronged approach likely to be more successful and efficacious than either therapeutic alone. It is well known that a major limitation to current cancer treatment is the limited activity of 'standard' chemotherapeutics against those tumour cells towards the centre of the mass because of diffusional limitations (Minchinton & Tannock, 2006). The dual VDA and cytotoxic approach would effectively overcome this limitation, with the VDA destroying those 'hard-to-reach' cancer cells from mid-tumour towards periphery (via shutdown of tumour blood vessels), and the cytotoxic chemotherapeutic destroying the VDA-resistant cells of the tumour viable rim. As described recently by Song et al., the VDA serves as a "cannon" eradicating many tumour cells without the requirement to interact with them, whereas the conventional cytotoxic chemotherapeutic concomitantly serves as a "pawn" by killing tumour cells in close proximity to blood vessels and within the drugs diffusional parameters (Song et al., 2016). With this co-administration strategy there is potential that drug doses may also be lower due to a lack of necessity to inherently compensate for difficulties in drug penetration. Furthermore, the inherent activity of VDAs to collapse tumour blood vessels has the added benefit of also entrapping drugs within the tumour mass and retarding their diffusion away from this site. Such an approach has been exemplified by the recently identified tumour-activated VDA, ICT2588 (Atkinson et al., 2010; Gill et al., 2014).

With regards combination therapy with VDAs, there are several chemotherapeutic classes which could be used, each with their advantages and disadvantages in terms of cardiovascular toxicities (Table 1). Several of these therapeutics are discussed in this context below.

2.2.1. Potential and risk for co-administration of VDAs and conventional chemotherapeutics

The fact that VDAs need to be administered concomitantly with therapeutics to tackle the "viable rim" of the tumour introduces several confounding factors to their putative success, not least the significantly elevated risk of additive or synergistic deleterious effects upon normal body systems. As clearly demonstrated in this review, cardiotoxicity is an issue associated with the vast majority of conventional chemotherapeutics and the VDAs. In essence cardiotoxicity induced by cancer therapeutics is a consequence of either direct cytotoxicity to cardiomyocytes (and other cardiac cell types, such as fibroblasts and pericytes) and the limited regenerative capacity therein, drug-induced perturbations of cardiac excitation-contraction coupling, induction of structural cellular changes and hypertrophic responses, effects upon the wider cardiovascular system, or combinations of these. This thereby raises the question as to whether co-administration of VDAs and conventional chemotherapeutics is wise and the risk manageable.

2.2.2. Benefits of vascular disruption for co-administration of chemotherapeutics

As is the case with all of the 'standard' cytotoxic chemotherapies, strategies which modify, reduce, or limit exposure of the cardiovascular system to the detrimental agents, whilst maintaining high enough drug levels to deliver therapeutic efficacy against the cancer is an idealistic target. The cannon and pawn approach (Song et al., 2016) precipitates the need for any concomitant chemotherapy to focus specifically on the viable tumour rim and not be hindered by modification of doses to facilitate efficacious drug levels throughout the tumour. In essence this would equate to systemic delivery of lower but highly efficacious concentrations of toxic chemotherapeutic, thereby reducing cardiac drug exposures.

Targeting of the viable rim by chemotherapeutics, ideally at modified concentrations, necessitates careful consideration of the administration schedules and the actual mechanism of the additional therapeutic agent (Fruytier et al., 2016; Martinelli et al., 2007). The vast majority of studies to date support administration of the VDA prior to the chemotherapeutic, causing a reduced requirement for the chemotherapeutic to reach the tumour 'core' and exclusively target the viable tumour rim. The outcome is heavily dependent upon the degree of effect the VDA has upon the tumour, and the microenvironmental changes secondary to VDA-induced blood flow (Fruytier et al., 2016). Of pertinence to cardiovascular toxicities of combination therapy, the

intervals between the two therapeutics is believed to be highly important with strong potential for crossover of acute toxicity profiles.

Several studies have now also suggested that the effects of the additional chemotherapeutic could be further potentiated through the VDA-mediated 'trapping' of the drug within the tumour, resulting in increased tumour drug exposures (Atkinson et al., 2010; Martinelli et al., 2007; Siemann, 2011). Such a mechanism would be seen as beneficial in terms of cardiotoxicity, through reduction in systemic drug levels and modulation of pharmacokinetics and subsequent cardiac exposure levels. However, despite offering significant potential from a cardiovascular toxicity mitigation perspective, the VDA-mediated trapping of the chemotherapeutic could have both positive and negative connotations for therapeutic efficacy. These responses are multifactorial and dependent upon both of the drugs that are administered and their dosing schedules. The significance of this for cardiovascular toxicity is as yet unknown.

3. Cardiovascular toxicity of alkylating agents

Alkylating agents, which bind DNA and inhibit its replication, have widespread application in cancer treatment (Todd, Groundwater, & Gill, 2017). The archetypal nitrogen mustard alkylating agents, cyclophosphamide and its structural analogue ifosfamide, are generally well tolerated at lower doses. However, in many cases, high-dose regimens are required and this is commonly associated with presentation of acute cardiotoxicity (Curigliano et al., 2012; Yeh & Bickford, 2009). Symptomatically this presents within two weeks post-administration as a combination of cardiac affects, including arrhythmias, left ventricular dysfunction, and congestive heart failure, with considerable morbidity and mortality reported (Curigliano et al., 2012). To date, there are no significant cases reported of longer term or late-stage chronic cardiotoxicity with cyclophosphamide or ifosfamide. The mechanisms responsible for acute cardiotoxicity remain unconfirmed, but are postulated to be a consequence of direct endothelial damage, extravasation of the drug and subsequent toxicity against cardiomyocytes, intracapillary microemboli and ultimately cardiac ischaemia (Curigliano et al., 2012; Jones & Ewer, 2006). Consequently, cardiotoxicity in the case of cyclophosphamide and ifosfamide is accepted as being due to administration of high-dose therapy rather than as a result of cumulative therapeutic dose, and thus theoretically could be reduced through modification of dosing regimens.

Platinum containing alkylating agents, specifically cisplatin and its analogues carboplatin and oxaliplatin, form inter-and intra-strand crosslinks with DNA, and are often administered alongside other chemotherapeutic drug classes. In contrast to the nitrogen mustard alkylating agents, cisplatin treatment is associated with dose-limiting acute and cumulative cardiovascular toxicity. Platinum-induced acute cardiotoxic events include abnormalities of ventricular repolarisation, depressed contractility, myocarditis, thromboembolic events, and dysrhythmias (Oun & Rowan, 2017; Patane, 2014; Yeh & Bickford, 2009). Although the mechanism underpinning platinum-induced acute cardiotoxicity is not fully resolved, it is hypothesised to be a consequence of direct damage of the vascular endothelium, induction of oxidative stress and a prothrombic state, and platinum-driven mitochondrial ultrastructural abnormalities and cellular stress (Altena et al., 2011; El-Awady el, Moustafa, Abo-Elmatty, & Radwan, 2011; Patane, 2014). Additional to acute cardiotoxic effects, cisplatin is also associated with delayed cardiotoxicity and increased risk for myocardial infarction over subsequent years (Gietema et al., 2000; Meinardi et al., 2000; Patane, 2014), with cisplatin detectable in urine and blood plasma twenty years after treatment (Gerl & Schierl, 2000; Gietema et al., 2000).

3.1. Co-administration of VDAs and alkylating agents

The nitrogen mustard class of alkylating agent in combination with a VDA does not appear to have been appraised either preclinically or in clinical trials (see Table 1). In light of the severity of reported cardiotoxicities and the types of malignancy currently managed by these agents it is understandable why such a combination has not yet been evaluated. However, the potential for dose reduction as a consequence of VDA effects and focused targeting of the viable tumour rim is an intriguing concept.

With regards to platinum-containing alkylating agents, despite associations with both acute and cumulative cardiotoxicity, several studies have evaluated this class of agent alongside VDAs (Table 1). In preclinical studies, VDAs delivered concomitantly with platinum alkylating agents resulted in significant synergistic antitumour effects (Ma et al., 2012; Takahashi et al., 2016). In the majority of cases, translation of this into clinical trials reinforced the synergistic efficacy, with no evidence of extensive dose-limiting cardiovascular toxicities (Grossmann et al., 2012; Lickliter et al., 2010; Ma et al., 2012; Takahashi et al., 2016). Overall, the toxicity of VDAs in the presence and absence of platinum-containing chemotherapeutics was particularly consistent with VDA monotherapy, with a few exceptions (Blay et al., 2015). Although somewhat surprising that cardiovascular toxicities of platinum-containing drugs were not more prevalent when in combination with a VDA, it remains to be determined whether combination with a VDA modifies the risks of cisplatin-mediated delayed cardiotoxicity over subsequent years (Patane, 2014).

4. Cardiovascular toxicity of antimetabolites

The antimetabolite class of chemotherapeutic either mimic or prevent the cellular synthesis of nucleotides, required for the synthesis of DNA, exemplified by the pyrimidine antagonist cytarabine and the fluoropyrimidine 5-fluorouracil (5-FU)(Todd et al., 2017). Although generally well tolerated, these drugs can induce a spectrum of adverse cardiovascular effects, including vascular effects such as angina, hyper- and hypo-tension, heart failure, and cardiac effects including arrhythmias, cardiogenic shock and myocardial infarction (Brana & Tabernero, 2010; Depetris et al., 2018; Herrmann et al., 2016). The incidence of drug-induced cardiovascular toxicity is highly variable across studies, made worse by continuous infusion, concurrent treatment with other drugs, or co-existing cardiac disease (Depetris et al., 2018; Polk, Vaage-Nilsen, Vistisen, & Nielsen, 2013). From a mechanistic perspective, the pathogenesis of cardiovascular toxicity is not yet resolved, with vasoconstriction being the main candidate, supported by endothelial damage, impairment of the antioxidant defence system, oxidative stress, and direct myocardial damage (Depetris et al., 2018; Herrmann et al., 2016).

4.1. Co-administration of VDAs and antimetabolites

To date there are no reports describing clinical administration of a VDA and either 5-FU or capecitabine (the prodrug of 5-FU). Although a study has evaluated Oxi4503 co-administration with cytarabine (Table 1), this was against leukaemia and thus Oxi4503 in this case would not have been acting as a VDA (Watts et al., 2017). Nevertheless, no indication of additional drug-induced cardiotoxicity was reported (Watts et al., 2017). In light of the exiguity and controversy in data surrounding the mechanistic basis of cardiovascular toxicity of the antimetabolites it is difficult to postulate or extrapolate the risk and benefits for co-administration of VDAs with these agents.

5. Cardiovascular toxicity of drugs disrupting topoisomerase activity

Topoisomerase type I (TOPI) and type II (TOPII) enzymes are ubiquitously expressed in mammalian cells, wherein they function to modulate DNA coiling and structure permissive of DNA replication, transcription, and chromosome organisation, via either single or double strand breaks, respectively (Delgado, Hsieh, Chan, & Hiasa, 2018; Todd et al., 2017). Topoisomerase-targeted drugs are exquisitely selective, as TOPI poisons do not affect TOPII and vice versa, and they function

as poisons rather than catalytic inhibitors, culminating in the induction of DNA damage and cell death (Delgado et al., 2018; Nitiss, 2009; Pommier, 2013). Administration of drugs targeted at topoisomerases is associated with development of secondary malignancies (Delgado et al., 2018; Pendleton, Lindsey, Felix, Grimwade, & Osheroff, 2014) and cardiovascular toxicity (Delgado et al., 2018), the latter of which is of major significance for VDA co-administration and is detailed below.

5.1. Topoisomerase I targeted agents

Targeting topoisomerase I (TOPI) is a proven strategy for management of a number of malignancies, with semisynthetic camptothecin derivatives, topotecan and irinotecan, approved for clinical use (Delgado et al., 2018; Martino et al., 2017). The incidence of cardiovascular toxicity with these agents is extremely rare, with no reported cases of topotecan-induced cardiovascular toxicity, and only an isolated case of irinotecan-induced bradycardia reported in the literature (Miya et al., 1998). To date, no chronic cardiovascular toxicities of these drugs has been reported either. This lack of apparent cardiovascular toxicity may purely be a consequence of reduced life expectancy or limited numbers of patients receiving these therapies, or simplistically the fact that no study has yet appraised longer-term toxicity follow-up of this patient population.

5.1.1. Co-administration of VDAs and topoisomerase I poisons

Current evidence would suggest that combination with VDAs would not precipitate any additional risk of cardiotoxicity. However, the potential to administer lower doses of TOPI-targeted drugs would negate impact of their short drug half-lives, and would theoretically reduce dose-limiting toxicities and permit curative doses to be delivered. Although, limitations due to chemical instability and inherent resistance of tumours to this class of agent would impact upon the overall VDA co-administrative strategy.

5.2. Topoisomerase II targeted agents

Drugs targeting TOPII are the commonest cytotoxic treatment used in the clinic for the management of a wide-range of adult and paediatric malignancies (Todd et al., 2017). Clinically-approved TOPII drugs affect the activities of both TOPIIα and TOPIIβ and encompass the anthracyclines (e.g. doxorubicin, epirubicin and daunorubicin), etoposide, and mitoxantrone (Delgado et al., 2018; Nitiss, 2009; Pommier, 2013). However, despite these therapeutics being potent and widely used cancer therapeutics, their use is undeniably associated with detrimental effects upon the cardiac system and significant concerns are now being raised regarding the aftermath of chemotherapeutic-treatment.

Anthracyclines are the mainstay of many cancer treatment regimes, with doxorubicin being the most commonly used. The major risk factor for development of doxorubicin-induced cardiac dysfunction is now known to be the cumulative drug exposure, with the incidence of clinical heart failure with doxorubicin treatment is reported to rise exponentially from 5% with a cumulative dose of 400 mg/m^2 to 48% with 700 mg/m^2 (Henriksen, 2018). The risk is further increased in older patients, when given as a component of multi-modality or multi-agent therapeutic approaches (Jiang, Mohan, Endo, Shen, & Wu, 2018; Lotriont e et al., 2013). However, despite limiting total cumulative doxorubicin exposure to 450 mg/m^2 resulting in less acute cardiovascular toxicity events, no significant reduction in late-onset complications has been reported, implicating that no dose of doxorubicin is inherently safe for the cardiovascular system (Cappetta et al., 2018; Lipshultz et al., 2005). Therefore, although cumulative dose is inherently related to development of cardiovascular toxicity, several other contributory factors are now known to be involved, including dosing rate and schedule, patient age, female gender, hypertension, previous cardiovascular disease, and genetic predisposition (Brana & Tabernero, 2010; Cappetta et al., 2018; Lipshultz, Cochran, Franco, & Miller, 2013; Lotriont e et al., 2013).

There are several hypotheses proposed to explain the mechanistic basis for doxorubicin-induced cardiotoxicity, including iron-mediated generation of reactive free radicals, specific interactions with TOPIIβ, drug-induced mitochondrial dysfunction, and perturbation of mitochondrial topoisomerase (mTOP) activity (Cappetta et al., 2017; Cappetta et al., 2018; Khiati et al., 2014; Octavia et al., 2012; Piegari et al., 2013; Renu, Abilash, Tirupathi, & Arunachalam, 2018; Vejpongsa & Yeh, 2014). Although it is highly likely these effects are not exclusive and that multiple mechanisms drive anthracycline-induced cardiotoxicity.

Similar to anthracyclines, the anthraquinone mitoxantrone (MTX) also induces cumulative and dose-dependent cardiotoxicity, somewhat unsurprising in light of the fact that mitoxantrone was developed as a synthetic doxorubicin analogue, albeit supposedly with decreased cardiotoxicity (Damiani et al., 2016). Although cardiotoxicity was initially reportedly lower for mitoxantrone relative to doxorubicin, a recent paediatric study indicates the contrary with mitoxantrone being associated with a higher risk for late-stage cardiotoxicity than doxorubicin (Feijen et al., 2019). Nevertheless, it is likely that the mode of cardiotoxic action of mitoxantrone and the anthracyclines is similar (Damiani et al., 2016).

In contrast to mitoxantrone and anthracyclines, etoposide shows minimum or no cardiovascular toxicity and very rarely drug-induced arrhythmias (Airey, Dodwell, Joffe, & Jones, 1995; Dorigo, Mansberg, & Kwan, 1993; Escoto, Ringewald, & Kalpatthi, 2010; Kridis, Khanfir, Triki, & Frikha, 2013). However, etoposide has been associated with development of vasospastic angina, hypotension and myocardial infarction, implying a vascular toxicity risk for this drug (Airey et al., 1995; Escoto et al., 2010; Schwarzer, Eber, Greinix, & Lind, 1991; Yano & Shimada, 1996). Effects upon atrial electroconductivity are also reported when etoposide is given in combination with the alkylating agent cisplatin (Kucharz et al., 2016). In most cases, it is highly likely that cardiovascular toxicities associated with etoposide are synergistic with or caused by the concomitant medications rather than other predisposing factors.

5.2.1. Co-administration of VDAs and topoisomerase II targeted agents

The co-administration of VDAs and the widely used anthracyclines has not yet been appraised clinically (Table 1). However, this combination offers significant therapeutic potential from an oncological standpoint, as indicated preclinically in sarcoma (Atkinson et al., 2010; Gill et al., 2014) and colon tumours (Song et al., 2016).

In terms of oncology chemotherapy, anthracyclines are exquisitely associated with cardiovascular toxicity, with both acute and chronic effects well documented. It is without doubt that the cumulative dose of anthracyclines is the major issue to address in terms of longer term adverse and life-threatening effects. The potential offered by VDAs to reduce overall anthracycline exposure as a consequence of necessity to just target the tumour cells within the post-VDA viable tumour rim, rather than penetrate deep into the tumour, is therefore attractive. Such a strategy and strong support for this is evidenced in the study of the VDA prodrug ICT2588 alongside doxorubicin, wherein lower doses of doxorubicin were shown to be efficacious and relevant (Atkinson et al., 2010; Gill et al., 2014). If translated to the clinic, a highly likely prospect, this would also result in a reduction in total exposure levels to the anthracycline (and mitoxantrone), the main factor behind the significant cardiovascular toxicity of this class of compound.

The inherent low risk of etoposide-induced cardiovascular toxicity would support its therapeutic use alongside VDAs. Interestingly, preclinical studies have shown that repeated low-dose etoposide treatment impairs the angiogenic potential of endothelial cells, associated with increased sensitivity to vascular-disrupting effects of chemotherapy (Pasquier et al., 2013). Therefore, despite its individual 'cardiac safety profile', etoposide may have an extra benefit in that it could further

reduce any VDA-induced cardiovascular toxicity. Improved understanding of these mechanisms, their clinical validity and significance is thereby warranted in order to mitigate for the risk of VDA-etoposide treatment regimens.

6. Cardiovascular toxicity of microtubule binding agents: Taxanes

Taxanes are used widely in the treatment of breast, ovarian and non-small cell lung cancers, wherein they exert their action by binding to microtubules and promoting their polymerisation and inactivation, culminating in mitotic arrest and cell death (Todd et al., 2017). Cardiac complications of these agents, specifically paclitaxel and docetaxel, include arrhythmias and cardiac ischaemia. The most common effect of these drugs upon the heart is transient sinus bradycardia, occurring in approximately one-third of patients during infusion, as a consequence of a direct chronotropic effects upon the Purkinje system. Drug-induced cardiac ischaemia is also reported for the taxanes, occurring in 5% and 2% of patients with paclitaxel and docetaxel, respectively (Rowinsky et al., 1991), However, unlike bradycardia which is a direct effect, taxane-induced ischaemia is associated with established cardiac disease. Notably, taxane-mediated heart failure is particularly associated with patients receiving prior anthracycline therapy (Sessa & Pagani, 2001), delaying the catabolism of anthracyclines and causing a greater reduction in the left ventricular ejection fraction (Minotti et al., 2001). The formulation of taxanes into Cremaphor EL, a polyoxyethylated castor oil vehicle, is also proposed to contribute to their cardiovascular toxicity, as it is recognised to stimulate histamine release and thus hypothesised to increase myocardial oxygen demand, coronary vasoconstriction, and changes in cardiac chronotrophy (Gelderblom, Verweij, Nooter, & Sparreboom, 2001).

6.1. Co-administration of VDAs and taxanes

Several studies have appraised VDAs alongside taxanes, notably docetaxel or paclitaxel (Table 1). In clinical trials appraising ABT-751 and docetaxel against advanced prostate cancer there were no clinically evident cardiovascular adverse events associated with treatment (Michels et al., 2010), with the caveat that cardiac function was not formally assessed in these trials. Similarly, fosbretabulin (CA4P) in combination with carboplatin and paclitaxel in advanced cancer patients did not result in any significant adverse cardiac effects, above those expected for each drug alone (Garon et al., 2016; Rustin et al., 2010; Zweifel et al., 2011).

Combination treatment of ombrabulin (AVE8062) and docetaxel was deemed superior to either agent alone in preclinical studies (Eskens et al., 2014; Nishio et al., 2018). In clinical trials of ombrabulin and docetaxel, no indication of additional chronic or delayed toxicities were observed (Eskens et al., 2014; Sessa et al., 2013). This included an absence of cardiac ischaemia, cardiac decompensation, drug-induced dysrhythmias, or cardiac biomarker abnormalities, and no promotion of hypertension in patients with a hypertensive history. In contrast to these initial studies, a recent trial of ombrabulin and docetaxel conducted in Japanese patients did report development of severe dose-limiting toxicities, although none were attributed to cardiovascular events (Nishio et al., 2018). The study claimed docetaxel clearance was reduced by co-administration of ombrabulin, with subsequently increased prevalence of taxane-mediated toxicities (Nishio et al., 2018).

To date, no negative associations have been reported between VDAs and taxanes in terms of the cardiovascular system in clinical studies, with the implication that no cardiac restrictions or limitations are required for their co-administration (Eskens et al., 2014). In addition, the VDA-facilitated potential for reduction in administered taxane dose also has beneficial potential for reducing the adverse cardiac effects observed with taxanes alone (Minotti et al., 2001; Rowinsky et al., 1991; Sessa & Pagani, 2001).

7. Cardiovascular toxicity of microtubule binding agents: Vinca alkaloids

Targeting and disruption of tubulin function is a successful and efficacious strategy for cancer therapy across many tumour types (Todd et al., 2017). The vinca alkaloids (Vincristine, Vinblastine and analogues) bind to cellular microtubules, similar to taxanes and colchicine-like VDAs, albeit it at different binding sites (Todd et al., 2017). In contrast to microtubule stabilisation induced by taxanes, these drugs depolymerise and destabilise the mitotic spindle, ultimately resulting in cell cycle arrest and cell death (Coderch, Morreale, & Gago, 2012; Martino et al., 2018).

Cardiovascular toxicity caused by vinca alkaloids is primarily vasorestrictive in nature, including angina, hypertension, myocardial ischaemia and myocardial infarction (Floyd et al., 2005). Alongside reversibility in drug-induced ECG perturbations, vinca-induced coronary spasm and subsequent cardiac ischaemia are rationalised as the driver for cardiovascular toxicities of this class of cancer chemotherapeutic (Herrmann et al., 2016). Such a theory is reinforced by a reported increased risk of ischaemic complications with vinca alkaloid administration in patients with established coronary artery disease (Herrmann et al., 2016).

7.1. Co-administration of VDAs and vinca alkaloids

There are no reports in the literature detailing clinical administration of a VDA and a vinca alkaloid, and subsequently no clinical reports describing toxicities of co-administration.

However, a recent preclinical study against hepatocellular carcinoma showed that administration of fosbretabulin alongside vincristine resulted in an augmented therapeutic effect relative to either agent alone *in vivo* (Aboubakr, Taye, Aly, Gamal-Eldeen, & El-Moselhy, 2017). Although effects upon the cardiovascular system were not specifically evaluated, increased vascular effects and elevated levels of reactive oxygen species, were measurable within the wider hepatic environment (Aboubakr et al., 2017). This highlights questions regarding their safe clinical use in combination.

The potential for administration of lower doses of a vinca alkaloid, due to the mechanistic activity of the VDA, provides scope to improve clinical efficacy and theoretically reduce dose-limiting toxicities of this drug class. However, a potential caveat to co-administration is that both drug classes function to destabilise microtubule dynamics (as opposed to the taxanes), albeit through different mechanisms (Coderch et al., 2012). Although the similarity of therapeutic mechanism could affect therapeutic efficacy, especially in light of genomic instability and acquisition of drug resistance, it is unlikely to play a major role in off-target effects against normal tissues.

8. Molecular targeted therapies

The most recent efforts in anti-cancer therapeutics have been toward the development of molecular targeted therapies. The theory behind this effort is that by making cancer therapeutics more targeted, inhibiting specific molecular targets instead of generalised DNA interaction, some of the toxicities seen with conventional cytotoxic chemotherapeutics could be eliminated or at least ameliorated. This unfortunately has not been the case for many chemotherapy-related toxicities, cardiovascular toxicity included. Many of these molecular-targeted agents have demonstrated adverse effects upon the heart, from mild electrophysiological changes, to myocarditis and fatal heart failure (Bellinger et al., 2015; Varricchi, Galdiero, & Tocchetti, 2017). The rationale for co-administration of these agents with VDAs in order to target the viable tumour rim is not evidentially strong. The cardiovascular toxicity mechanisms of these molecular-targeted agents is likely diverse, but is largely outside the scope of this review and is extensively addressed elsewhere (Bellinger et al., 2015; Florido, Smith, Cuomo, &

Russell, 2017; Rhea & Oliveira, 2018; Varricchi, Galdiero, & Tocchetti, 2017). However, therapeutic approaches of relevance and interest for co-administration with VDAs are briefly described below.

8.1. Anti-angiogenic agents

Tumour growth, invasion, dissemination and overall survival are dependent upon the existence of a viable and functional vascular and lymphatic network, which develop from the host vasculature via the angiogenic process (Tozer et al., 2005; Weis & Cheresh, 2011). There are now several strategies proposed for the targeting and interference of the angiogenesis process and thus prevention of tumour expansion and dissemination. The most notable strategies being sequestering vascular endothelial growth factor (VEGF) and prevention of its binding to the cell-surface receptor VEGFR (e.g. the monoclonal antibody bevacizumab), and inhibition of downstream signalling from VEGFR and other similar receptors (e.g. the tyrosine kinase inhibitors such as axitinib, pazopanib, sorafenib, and sunitinib) (Weis & Cheresh, 2011). Not surprisingly, many of the anti-angiogenic drugs have reported close relationships to cardiovascular toxicity, both asymptomatically and symptomatically, with hypertension being a major issue with both VEGF-sequestering and kinase inhibitor classes of these agents (Faruque et al., 2014). Although not yet conclusively proven, it is highly likely that these cardiovascular toxicities are a result of direct effects upon the vasculature and subsequent hypertension, cardiac strain and heart failure, in conjunction with effects upon the renal system (Cosmai, Gallieni, & Porta, 2015; Di Lorenzo et al., 2009). Such a hypothesis is supported by the fact that cardiovascular toxicity induced by these agents is higher in patients with pre-existing cardiovascular risk factors (Chu et al., 2007; Di Lorenzo et al., 2009; Grisham et al., 2018; Rhea & Oliveira, 2018).

8.1.1. Co-administration of VDAs and anti-angiogenic agents

Despite anti-angiogenic agents and VDAs both hitting tumour vasculature, their marked differences in mechanism and target offers the opportunity for a two-pronged attack on the tumour and a different therapeutic approach (Siemann et al., 2017). Simplistically, this strategy rationale is to destroy existing vasculature and concomitantly prevent the development of new supportive blood vessels requested by the tumour, which as a minimum would be cytostatic for the tumour and retard any further tumour growth. Additional to the mechanistic differences, the anti-angiogenic also serves to prevent revascularisation during and after treatment with the VDA (Siemann et al., 2017). However, as is the case with VDAs, anti-angiogenic monotherapy is highly unlikely to be curative even when given at high doses or for a prolonged period of time. Similarly, although combination therapy offers promise, with the VDA targeting the tumour core and antiangiogenic therapy inhibiting neovascularisation, the viable tumour rim is still highly likely to survive. Consequently, these therapies are suggested to be positioned as maintenance therapy in patients previously administered other chemotherapeutics, with the objective of improving progression free survival (Fabi et al., 2012; Siemann et al., 2017).

Several preclinical studies have indicated a marked improvement in tumour response for co-administration of an anti-angiogenic drug and a VDA, relative to either agent alone (Siemann et al., 2017). These results and others subsequently led to several clinical trials evaluating the archetypical anti-angiogenic angtibody bevacizumab (Avastin) alongside a VDA (Table 1). For the vast majority of studies, this dual anti-vascular approach was well tolerated and improvements in progression free survival were observed (Siemann et al., 2017). In a phase II clinical trial in chemotherapy-naiive lung cancer, fosbretabulin in combination with bevacizumab, carboplatin (alkylating agent), and paclitaxel (antimicrotubule agent) similar drug-induced adverse events were observed between all treatment groups. No differences in serious adverse events or early discontinuations from the trial were observed between groups receiving CA4P and those not (Garon et al., 2016; Siemann et al., 2017). Of note in all reported studies to date of bevacizumab and a VDA is the fact that hypertension is the most common dose-limiting toxicity, albeit of an increased magnitude than bevacizumab alone (Grisham et al., 2018; Nathan et al., 2012). Whilst bevacizumab primarily causes sustained hypertension requiring modulation of hypertensive medication, the elevated blood pressure observed with the VDA is acute and managed with either pre-treatment or immediate administration of hypertensive medication at the time of initial blood pressure rise (Grisham et al., 2018). Despite several trials demonstrating promising and encouraging results for co-administration of a VDA and bevacizumab, it remains to be determined whether this treatment regimen is optimal in terms of efficacy, or whether assessment on a wider patient population would identify further issues.

Although several studies have appraised bevacizumab combination therapy with VDAs, few studies have evaluated VDAs alongside small molecule VEGF-signalling pathway inhibitors. In preclinical studies, the VDA BNC105 potentiates the activity of pazopanib against renal cancer (Inglis et al., 2014) and co-administration of OXi4503 and sunitinib results in improved efficacy against colorectal liver metastasis (Nguyen, Fifis, & Christophi, 2016). In both studies no obvious clinical signs of cardiotoxicity were observed. Recently, this treatment approach has been translated to the clinic as a phase 1b/II trial of fosbretabulin and pazopanib against ovarian cancer (Morgan et al., 2018). However, although improved therapeutic efficacy was indicated, several patients developed acute hypertension plus secondary cardiac toxicity, resulting in premature discontinuation of the trial (Morgan et al., 2018). Further studies are therefore required to characterise the mechanistic basis of this unacceptable toxicity, and ascertain the cardiotoxicity safety profile of combination treatment with VDAs and anti-angiogenic approaches. Consequently, until further refined and understood, the detrimental cardiotoxic risk of these agents is likely to preclude their use in combination therapies with VDAs.

8.2. Cardiovascular toxicity of immune checkpoint inhibitors and implications for VDA co-treatment

In addition to the development of therapeutics activating or inactivating signalling pathways, in response to defined mutations (i.e. molecular-targeted therapies), advances in molecular immunology unveiling the mechanisms driving cellular immune response have now led to a new class of therapeutic termed immune checkpoint inhibitors (Sharma & Allison, 2015a, 2015b). These therapeutic antibodies, targeting either cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) or its ligand (PD-L1), have demonstrated excellent clinical success against a diverse range of malignancies (Sharma & Allison, 2015a; Varricchi et al., 2017). However, the downside to the high-ranking success of immune checkpoint inhibitors is their wide-spectrum of immune-related adverse effects, including effects upon the heart (Varricchi, Galdiero, Marone, et al., 2017; Varricchi, Galdiero, & Tocchetti, 2017). In particular, immune checkpoint inhibitors have been shown to cause myocarditis and fatal heart failure, both when administered alone and in combination with other therapeutics (Varricchi, Galdiero, Marone, et al., 2017; Varricchi, Galdiero, & Tocchetti, 2017).

The co-administration of immune checkpoint inhibitors alongside VDAs has been proposed as a strategy to improve treatment success and VDA efficacy, with the rationale that the VDA will damage tumour blood vessels and encourage lymphocytic infiltration and subsequent tumour destruction (Inglis, Beaumont, Leske, Scherer, & Lavranos, 2016; Missiaen, Mazzone, & Bergers, 2018). The Australasian MODULATE clinical trial, initiated in early 2019, is investigating whether a VDA (BNC105) in combination with an immunotherapeutic agent (nivolumab) can be used to treat advanced colorectal cancer. Based on the emerging novel cardiotoxicty profile of immune checkpoint inhibitors and hypertensive response associated with VDAs, outcomes from this combination study are eagerly awaited.

9. Conclusion: VDAs and cancer therapy, good or bad in terms of cardiovascular toxicity?

The potential for VDAs as a viable therapeutic option for the treatment of solid tumours has been clearly qualified by numerous preclinical studies and early stage clinical trials. From a therapeutic perspective, despite demonstrating clear promise, the existence of a viable rim of tumour cells following VDA monotherapy thereby means the clinical efficacy of VDAs are dependent upon co-administration of an additional chemotherapeutic agent to target these surviving tumour cells. Although such a treatment model has demonstrated exquisite preclinical therapeutic effects, including tumour eradication and the potential for dose reduction of chemotherapeutics, the potential for exacerbating off-target cardiovascular toxicity of cancer therapeutics was raised as a concern.

Detrimental effects upon the cardiovascular system are a common occurrence across the diverse spectrum of cancer chemotherapeutics. Effects upon the cardiac system itself and the wider vasculature are evident, ranging from overt toxicity and structural cardiac changes, to alterations in cardiac contractility and the development of drug-induced dysrhythmias, through to induction of vascular contractility and subsequent haemodynamic changes. In the case of VDAs, the most prevalent cardiovascular effect is acute haemodynamic change occurring immediately after administration, with resolution within the subsequent following few hours. On the whole, cardiovascular effects of VDAs are generally transient and manageable with standard cardiac medication, and with frequent monitoring of blood pressure whilst receiving VDA therapy. Consequently, VDA-induced cardiovascular toxicity per se is not deemed a hidden evil, but rather a manageable risk. The complication arises when the VDA is administered alongside a chemotherapeutic which itself exhibits detrimental effects upon the heart, with the cardiovascular toxicity effects of each agent potentially multiplying each other. Although each class of chemotherapeutic with potential for VDA co-administration exhibits slightly different risk, as described above, in several cases this is a consequence of delivery of high-dose (e.g. alkylating agents) or cumulative dose (e.g. anthracyclines). In principle, these toxicities may be mitigated when delivered alongside a VDA wherein a lower dose of the cytotoxic chemotherapeutic agent may be possible due to the requirement to only 'hit' those cells in the viable tumour rim.

The vast majority of cardiotoxic effects observed with cancer chemotherapeutics are reportedly acute or early onset in nature, with their identification and subsequent management easier to identify and plan. However, as is evident with anthracyclines, drug-induced cardiotoxicity in some cases may present several years after administration. This is problematic in that cardiac damage and effects remain 'silent' and only present as fairly late stage cardiac failure. The emergence of these delayed toxicities is a consequence of significant improvements in cancer therapy and the consequent prolongation in patient survival. It remains to be ascertained whether non-anthracycline chemotherapy classes, including VDAs, also associate with delayed cardiotoxicity. Furthermore, whether combination therapy of VDAs and chemotherapeutics promote or retard delayed and late-stage cardiotoxicity can as yet not be predicted. The occurrence of these delayed effects will only become evident through increases in patient survival and subsequent clinical presentation of cardiological effects, at which point it maybe too late to prevent or reverse these effects. Therefore, a deeper understanding and appreciation of the off-target effects of such therapies and molecular mechanisms will be essential to predicting and potentially treating cardiovascular toxicities of all cancer chemotherapeutic approaches, including VDAs.

One factor appearing as a constant aggravator of cardiovascular toxicity, especially in the case of detrimental effects upon the vascular system, is pre-existing cardiac disease. Clinical use of many cancer chemotherapeutics are strongly avoided in patients with cardiac comorbidities or coronary artery disease, unless the benefit exceeds the risk. It is therefore assumed that such a restriction would also be applicable to VDAs, not least because of the requirement for co-administration of additional chemotherapeutics. The caveat being that the effects of VDA upon the vasculature system appear to be transient in nature and occur across a short post-administration window. If effects of VDAs are manageable in this context, then the beneficial effects of lowering exposure to the additional chemotherapeutic may serve to circumvent the issues associated with treatment in this patient population.

The emergence of molecular-targeted therapies heralding a new wave of successes in terms of clinical efficacy of cancer is encouraging. The manageability of hypertensive effects associated with combination of VDAs with the anti-angiogenic agent bevacizumab is obviously very promising (Garon et al., 2016; Grisham et al., 2018; Siemann et al., 2017). However, unlike bevacizumab, the fact that trials of pazopanib in combination with fosbretabulin were prematurely terminated due to cardiac toxicities raises the concern regarding adoption and qualification of drug-specific versus therapeutic-pathway approaches for VDA combination therapy (Morgan et al., 2018). Similarly, in the context of molecular-targeted approaches, the severity of cardiotoxic effects caused by immune checkpoint inhibitors (Varricchi, Galdiero, Marone, et al., 2017) questions their suitability for combination with VDAs, a point that may be resolved once the outcomes of the MODULATE trial of BNC105 and nivolumab are reported. In the meantime, such combinations should be approached with trepidation.

9.1. VDAs and risk of cardiovascular toxicity: future directions?

Many issues remain to be resolved with VDAs in respect of their clinical validity for cancer management, treatment regimens, and the existence and severity of drug-induced adverse cardiovascular effects. In this context, the key issues that need to be addressed are i) the contributions played by the cardiac and vascular compartments in VDA-induced cardiovascular toxicities, and whether this generic or drug specific in terms of this drug class; ii) the true longevity of the haemodynamic effects of VDAs in the clinic and whether clinical management strategies, as adopted in the FOCUS trial (Monk et al., 2016), are sufficient to mitigate such risk; iii) Clinical studies to date support efficacy of a number of chemotherapeutic drugs for co-administration with VDAs in a cannon and pawn approach (Song et al., 2016), particularly platinum-containing alkylating agents, anthracyclines and taxanes. However, much of this is based on the assumption of effective dose-reduction due to VDA presence. Such a hypothesis therefore needs to be robustly addressed in order to qualify the potential for these combinations; and finally, iv) the greatest cardiovascular problem associated with cancer chemotherapy is delayed cardiotoxicity, appearing many years after cessation of treatment. It is therefore imperative that the underpinning mechanism for such effects is elucidated to fully appreciate and manage required cardiological interventions, with strategies for prediction and mitigation identified. Until such queries are addressed it would be difficult to fully assign cardiotoxic risk associations for VDAs or their inclusion in combination therapies. However, the evidence relating to effectiveness of the tubulin-interactive VDA as a therapeutic approach coupled to lower or manageable cardiotoxic risk is providing compelling arguments towards the incorporation of VDAs as a treatment option, albeit hinged upon clinical efficacy.

Acknowledgements

Kimberly L Rockley was funded by a Durham University Faculty PhD studentship; Carol De Santis is funded on a studentship through the Medical Research Council Integrated Toxicology Training Partnership; Asma K Mohamed is funded by a sponsored studentship from the Libyan Ministry of Higher Education and scientific research through the Faculty of Medicine at Omar Al-Mukhtar University.

Conflict of interests

JH Gill is a co-founder of Incanthera Ltd, a company with interests in cancer drug development, and is a named inventor on intellectual property relating to the development of cancer therapeutics. All other authors declare that there are no potential conflicts of interest.

References

Aboubakr, E. M., Taye, A., Aly, O. M., Gamal-Eldeen, A. M., & El-Moselhy, M. A. (2017). Enhanced anticancer effect of combretastatin A-4 phosphate when combined with vincristine in the treatment of hepatocellular carcinoma. *Biomedicine & Pharmacotherapy 89*, 36–46.

Airey, C. L., Dodwell, D. J., Joffe, J. K., & Jones, W. G. (1995). Etoposide-related myocardial infarction. *Clinical Oncology (Royal College of Radiologists) 7*, 135.

Alameddine, R. S., Yakan, A. S., Skouri, H., Mukherji, D., Temraz, S., & Shamseddine, A. (2015). Cardiac and vascular toxicities of angiogenesis inhibitors: The other side of the coin. *Critical Reviews in Oncology/Hematology 96*, 195–205.

Altena, R., Hummel, Y. M., Nuver, J., Smit, A. J., Lefrandt, J. D., de Boer, R. A., et al. (2011). Longitudinal changes in cardiac function after cisplatin-based chemotherapy for testicular cancer. *Annals of Oncology 22*, 2286–2293.

Anderson, H. L., Yap, J. T., Miller, M. P., Robbins, A., Jones, T., & Price, P. M. (2003). Assessment of pharmacodynamic vascular response in a phase I trial of combretastatin A4 phosphate. *Journal of Clinical Oncology 21*, 2823–2830.

Atkinson, J. M., Falconer, R. A., Edwards, D. R., Pennington, C. J., Siller, C. S., Shnyder, S. D., et al. (2010). Development of a novel tumor-targeted vascular disrupting agent activated by membrane-type matrix metalloproteinases. *Cancer Research 70*, 6902–6912.

Bagnes, C., Panchuk, P. N., & Recondo, G. (2010). Antineoplastic chemotherapy induced QTc prolongation. *Current Drug Safety 5*, 93–96.

Bahleda, R., Sessa, C., Del Conte, G., Gianni, L., Capri, G., Varga, A., et al. (2014). Phase I clinical and pharmacokinetic study of ombrabulin (AVE8062) combined with cisplatin/docetaxel or carboplatin/paclitaxel in patients with advanced solid tumors. *Investigational New Drugs 32*, 1188–1196.

Baluk, P., Hashizume, H., & McDonald, D. M. (2005). Cellular abnormalities of blood vessels as targets in cancer. *Current Opinion in Genetics & Development 15*, 102–111.

Barlow, K. D., Sanders, A. M., Soker, S., Ergun, S., & Metheny-Barlow, L. J. (2013). Pericytes on the tumor vasculature: jekyll or hyde? *Cancer Microenvironment 6*, 1–17.

Beerepoot, L. V., Radema, S. A., Witteveen, E. O., Thomas, T., Wheeler, C., Kempin, S., et al. (2006). Phase I clinical evaluation of weekly administration of the novel vascular-targeting agent, ZD6126, in patients with solid tumors. *Journal of Clinical Oncology 24*, 1491–1498.

Bellinger, A. M., Arteaga, C. L., Force, T., Humphreys, B. D., Demetri, G. D., Druker, B. J., et al. (2015). Cardio-oncology: How new targeted cancer therapies and precision medicine can inform cardiovascular discovery. *Circulation 132*, 2248–2258.

Blakey, D. C., Ashton, S. E., Westwood, F. R., Walker, M., & Ryan, A. J. (2002). ZD6126: a novel small molecule vascular targeting agent. *International Journal of Radiation Oncology, Biology, Physics 54*, 1497–1502.

Blay, J. Y., Papai, Z., Tolcher, A. W., Italiano, A., Cupissol, D., Lopez-Pousa, A., et al. (2015). Ombrabulin plus cisplatin versus placebo plus cisplatin in patients with advanced soft-tissue sarcomas after failure of anthracycline and ifosfamide chemotherapy: a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology 16*, 531–540.

Brana, I., & Tabernero, J. (2010). Cardiotoxicity. *Annals of Oncology 21*(Suppl. 7) (vii173-179).

Burge, M., Francesconi, A. B., Kotasek, D., Fida, R., Smith, G., Wilks, A., et al. (2013). Phase I, pharmacokinetic and pharmacodynamic evaluation of CYT997, an orally-bioavailable cytotoxic and vascular-disrupting agent. *Investigational New Drugs 31*, 126–135.

Cameron, A. C., Touyz, R. M., & Lang, N. N. (2016). Vascular complications of cancer chemotherapy. *The Canadian Journal of Cardiology 32*, 852–862.

Cappetta, D., De Angelis, A., Sapio, L., Prezioso, L., Illiano, M., Quaini, F., et al. (2017). Oxidative stress and cellular response to doxorubicin: A common factor in the complex milieu of anthracycline cardiotoxicity. *Oxidative Medicine and Cellular Longevity 2017*, 1521020.

Cappetta, D., Rossi, F., Piegari, E., Quaini, F., Berrino, L., Urbanek, K., et al. (2018). Doxorubicin targets multiple players: A new view of an old problem. *Pharmacological Research 127*, 4–14.

Cardinale, D., Biasillo, G., & Cipolla, C. M. (2016). Curing cancer, saving the heart: A challenge that cardioncology should not miss. *Current Cardiology Reports 18*, 51.

Chamberlain, M. C., Grimm, S., Phuphanich, S., Recht, L., Zhu, J. Z., Kim, L., et al. (2014). A phase 2 trial of verubulin for recurrent glioblastoma: A prospective study by the Brain Tumor Investigational Consortium (BTIC). *Journal of Neuro-Oncology 118*, 335–343.

Chase, D. M., Chaplin, D. J., & Monk, B. J. (2017). The development and use of vascular targeted therapy in ovarian cancer. *Gynecologic Oncology 145*, 393–406.

Chauhan, A., Arnold, S., Dressler, E., Nichols, D., & Anthony, L. (2018). A phase 1 study of fosbretabulin in combination with everolimus in neuroendocrine tumors (Grades 1-3) that have progressed after at least one prior regimen for metastatic disease. *Pancreas 47*, 334–335.

Chauhan, A., Arnold, S., Slone, S. A., Flynn, H., Weiss, H., & Anthony, L. B. (2018). A phase I/II study of fosbretabulin in combination with everolimus in neuroendocrine tumors that have progressed after at least one prior regimen for metastatic disease. *Journal of Clinical Oncology 36*.

Chen, M., Lei, X., Shi, C., Huang, M., Li, X., Wu, B., et al. (2017). Pericyte-targeting prodrug overcomes tumor resistance to vascular disrupting agents. *The Journal of Clinical Investigation 127*, 3689–3701.

Chu, T. F., Rupnick, M. A., Kerkela, R., Dallabrida, S. M., Zurakowski, D., Nguyen, L., et al. (2007). Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet 370*, 2011–2019.

Coderch, C., Morreale, A., & Gago, F. (2012). Tubulin-based structure-affinity relationships for antimitotic Vinca alkaloids. *Anti-Cancer Agents in Medicinal Chemistry 12*, 219–225.

Cogle, C. R., Gonzalez, A., Pettiford, L., Meacham, A., Wise, E., Norkin, M., et al. (2012). A phase i study of the vascular disrupting combretastatin, OXi4503, in patients with relapsed and refractory acute myeloid leukemia (AML) and Myelodysplastic Syndromes (MDS). *Blood*, 120.

Collins, I., & Workman, P. (2006). New approaches to molecular cancer therapeutics. *Nature Chemical Biology 2*, 689–700.

Conte, G. D., Bahleda, R., Moreno, V., Damian, S., Perotti, A., Lassau, N., et al. (2012). A phase I study of ombrabulin (O) combined with bevacizumab (B) in patients with advanced solid tumors (NCT01193595). *Journal of Clinical Oncology 30*, 3080.

Cooney, M. M., Radivoyevitch, T., Dowlati, A., Overmoyer, B., Levitan, N., Robertson, K., et al. (2004). Cardiovascular safety profile of combretastatin a4 phosphate in a single-dose phase I study in patients with advanced cancer. *Clinical Cancer Research 10*, 96–100.

Cosmai, L., Gallieni, M., & Porta, C. (2015). Renal toxicity of anticancer agents targeting HER2 and EGFR. *Journal of Nephrology 28*, 647–657.

Curigliano, G., Cardinale, D., Suter, T., Plataniotis, G., de Azambuja, E., Sandri, M. T., et al. (2012). Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. *Annals of Oncology 23*(Suppl. 7), vii155–166.

Curigliano, G., Mayer, E. L., Burstein, H. J., Winer, E. P., & Goldhirsch, A. (2010). Cardiac toxicity from systemic cancer therapy: a comprehensive review. *Progress in Cardiovascular Diseases 53*, 94–104.

Damiani, R. M., Moura, D. J., Viau, C. M., Caceres, R. A., Henriques, J. A., & Saffi, J. (2016). Pathways of cardiac toxicity: Comparison between chemotherapeutic drugs doxorubicin and mitoxantrone. *Archives of Toxicology 90*, 2063–2076.

Delgado, J. L., Hsieh, C. M., Chan, N. L., & Hiasa, H. (2018). Topoisomerases as anticancer targets. *The Biochemical Journal 475*, 373–398.

Depetris, I., Marino, D., Bonzano, A., Cagnazzo, C., Filippi, R., Aglietta, M., et al. (2018). Fluoropyrimidine-induced cardiotoxicity. *Critical Reviews in Oncology/Hematology 124*, 1–10.

Deryugina, E. I., & Quigley, J. P. (2015). Tumor angiogenesis: MMP-mediated induction of intravasation- and metastasis-sustaining neovasculature. *Matrix Biology 44-46*, 94–112.

Di Lorenzo, G., Autorino, R., Bruni, G., Carteni, G., Ricevuto, E., Tudini, M., et al. (2009). Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. *Annals of Oncology 20*, 1535–1542.

van Dijk, C. G., Nieuweboer, F. E., Pei, J. Y., Xu, Y. J., Burgisser, P., van Mulligen, E., et al. (2015). The complex mural cell: Pericyte function in health and disease. *International Journal of Cardiology 190*, 75–89.

Dorigo, A., Mansberg, R., & Kwan, Y. L. (1993). Lomustine, etoposide, methotrexate and prednisone (LEMP) therapy for relapsed and refractory non-Hodgkin's lymphoma. *European Journal of Haematology 50*, 37–40.

Dy, G. K., & Adjei, A. A. (2013). Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA: A Cancer Journal for Clinicians 63*, 249–279.

El-Awady el, S. E., Moustafa, Y. M., Abo-Elmatty, D. M., & Radwan, A. (2011). Cisplatin-induced cardiotoxicity: Mechanisms and cardioprotective strategies. *European Journal of Pharmacology 650*, 335–341.

Escoto, H., Ringewald, J., & Kalpatthi, R. (2010). Etoposide-related cardiotoxicity in a child with haemophagocytic lymphohistiocytosis. *Cardiology in the Young 20*, 105–107.

Eskens, F. A., Tresca, P., Tosi, D., Van Doorn, L., Fontaine, H., Van der Gaast, A., et al. (2014). A phase I pharmacokinetic study of the vascular disrupting agent ombrabulin (AVE8062) and docetaxel in advanced solid tumours. *British Journal of Cancer 110*, 2170–2177.

Fabi, A., Russillo, M., Ferretti, G., Metro, G., Nistico, C., Papaldo, P., et al. (2012). Maintenance bevacizumab beyond first-line paclitaxel plus bevacizumab in patients with Her2-negative hormone receptor-positive metastatic breast cancer: efficacy in combination with hormonal therapy. *BMC Cancer 12*, 482.

Faruque, L. I., Lin, M., Battistella, M., Wiebe, N., Reiman, T., Hemmelgarn, B., et al. (2014). Systematic review of the risk of adverse outcomes associated with vascular endothelial growth factor inhibitors for the treatment of cancer. *PLoS One 9*, e101145.

Feijen, E. A. M., Leisenring, W. M., Stratton, K. L., Ness, K. K., van der Pal, H. J. H., van Dalen, E. C., et al. (2019). Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. *JAMA Oncology*. https://doi.org/10.1001/jamaoncol.2018.6634 in press.

Florido, R., Smith, K. L., Cuomo, K. K., & Russell, S. D. (2017). Cardiotoxicity from human epidermal growth factor receptor-2 (HER2) targeted therapies. *Journal of the American Heart Association 6*, e006915.

Floyd, J. D., Nguyen, D. T., Lobins, R. L., Bashir, Q., Doll, D. C., & Perry, M. C. (2005). Cardiotoxicity of cancer therapy. *Journal of Clinical Oncology 23*, 7685–7696.

Fox, E., Maris, J. M., Widemann, B. C., Goodspeed, W., Goodwin, A., Kromplewski, M., et al. (2008). A phase I study of ABT-751, an orally bioavailable tubulin inhibitor, administered daily for 21 days every 28 days in pediatric patients with solid tumors. *Clinical Cancer Research 14*, 1111–1115.

Fruytier, A. C., Le Duff, C. S., Po, C., Magat, J., Bouzin, C., Neveu, M. A., et al. (2016). The blood flow shutdown induced by combretastatin A4 impairs gemcitabine delivery in a mouse hepatocarcinoma. *Frontiers in Pharmacology 7*, 506.

Furst, R., & Vollmar, A. M. (2013). A new perspective on old drugs: Non-mitotic actions of tubulin-binding drugs play a major role in cancer treatment. *Pharmazie 68*, 478–483.

Garon, E. B., Neidhart, J. D., Gabrail, N. Y., de Oliveira, M. R., Balkissoon, J., & Kabbinavar, F. (2016). A randomized Phase II trial of the tumor vascular disrupting agent CA4P (fosbretabulin tromethamine) with carboplatin, paclitaxel, and bevacizumab in

advanced nonsquamous non-small-cell lung cancer. *Onco Targets and Therapy 9*, 7275–7283.
Gelderblom, H., Verweij, J., Nooter, K., & Sparreboom, A. (2001). Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *European Journal of Cancer 37*, 1590–1598.
Gerl, A., & Schierl, R. (2000). Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. *Acta Oncologica 39*, 519–522.
Gietema, J. A., Meinardi, M. T., Messerschmidt, J., Gelevert, T., Alt, F., Uges, D. R., et al. (2000). Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. *Lancet 355*, 1075–1076.
Gill, J. H., Loadman, P. M., Shnyder, S. D., Cooper, P., Atkinson, J. M., Ribeiro Morais, G., et al. (2014). Tumor-targeted prodrug ICT2588 demonstrates therapeutic activity against solid tumors and reduced potential for cardiovascular toxicity. *Molecular Pharmaceutics 11*, 1294–1300.
Gould, S., Westwood, F. R., Curwen, J. O., Ashton, S. E., Roberts, D. W., Lovick, S. C., et al. (2007). Effect of pretreatment with atenolol and nifedipine on ZD6126-induced cardiac toxicity in rats. *Journal of the National Cancer Institute 99*, 1724–1728.
Gramza, A. W., Balasubramaniam, S., Fojo, A. T., Ward, J., & Wells, S. A. (2013). Phase I/II trial of crolibulin and cisplatin in solid tumors with a focus on anaplastic thyroid cancer: Phase I results. *Journal of Clinical Oncology 31*, 6074.
Greystoke, A., Blagden, S., Thomas, A. L., Scott, E., Attard, G., Molife, R., et al. (2006). A phase I study of intravenous TZT-1027 administered on day 1 and day 8 of a three-weekly cycle in combination with carboplatin given on day 1 alone in patients with advanced solid tumours. *Annals of Oncology 17*, 1313–1319.
Grisham, R., Ky, B., Tewari, K. S., Chaplin, D. J., & Walker, J. (2018). Clinical trial experience with CA4P anticancer therapy: Focus on efficacy, cardiovascular adverse events, and hypertension management. *Gynecologic Oncology Research and Practice 5*(1).
Grosios, K., Holwell, S. E., McGown, A. T., Pettit, G. R., & Bibby, M. C. (1999). In vivo and in vitro evaluation of combretastatin A-4 and its sodium phosphate prodrug. *British Journal of Cancer 81*, 1318–1327.
Grossmann, K. F., Colman, H., Akerley, W. A., Glantz, M., Matsuoko, Y., Beelen, A. P., et al. (2012). Phase I trial of verubulin (MPC-6827) plus carboplatin in patients with relapsed glioblastoma multiforme. *Journal of Neuro-Oncology 110*, 257–264.
Hande, K. R., Hagey, A., Berlin, J., Cai, Y., Meek, K., Kobayashi, H., et al. (2006). The pharmacokinetics and safety of ABT-751, a novel, orally bioavailable sulfonamide antimitotic agent: results of a phase 1 study. *Clinical Cancer Research 12*, 2834–2840.
He, X. X., Li, S., Huang, H., Li, Z. M., Chen, L. K., Ye, S., et al. (2011). A pharmacokinetic and safety study of single dose intravenous combretastatin A4 phosphate in Chinese patients with refractory solid tumours. *British Journal of Clinical Pharmacology 71*, 860–870.
Heist, R. S., Aren, O. R., Mita, A. C., Polikoff, J., Bazhenova, L., Lloyd, G. K., et al. (2014). Randomized phase 2 trial of plinabulin (NPI-2358) plus docetaxel in patients with advanced non-small cell lung cancer (NSCLC). *Journal of Clinical Oncology 32*.
Henriksen, P. A. (2018). Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention. *Heart 104*, 971–977.
Herrmann, J., Yang, E. H., Iliescu, C. A., Cilingiroglu, M., Charitakis, K., Hakeem, A., et al. (2016). Vascular toxicities of cancer therapies: The old and the new–an evolving avenue. *Circulation 133*, 1272–1289.
Hinnen, P., & Eskens, F. A. (2007). Vascular disrupting agents in clinical development. *British Journal of Cancer 96*, 1159–1165.
Ho, Y. J., Wang, T. C., Fan, C. H., & Yeh, C. K. (2017). Current progress in antivascular tumor therapy. *Drug Discovery Today 22*, 1503–1515.
Horti, J., Juhasz, E., Monostori, Z., Maeda, K., Eckhardt, S., & Bodrogi, I. (2008). Phase I study of TZT-1027, a novel synthetic dolastatin 10 derivative, for the treatment of patients with non-small cell lung cancer. *Cancer Chemotherapy and Pharmacology 62*, 173–180.
Inglis, D. J., Beaumont, D. M., Leske, A. F., Scherer, M. A., & Lavranos, T. C. (2016). BNC105 induces tumor micro environment changes which enhance the efficacy of checkpoint inhibitor therapy in preclinical models. *Cancer Research*, 76.
Inglis, D. J., Lavranos, T. C., Beaumont, D. M., Leske, A. F., Brown, C. K., Hall, A. J., et al. (2014). The vascular disrupting agent BNC105 potentiates the efficacy of VEGF and mTOR inhibitors in renal and breast cancer. *Cancer Biology & Therapy 15*, 1552–1560.
Jaroch, K., Karolak, M., Gorski, P., Jaroch, A., Krajewski, A., Ilnicka, A., et al. (2016). Combretastatins: In vitro structure-activity relationship, mode of action and current clinical status. *Pharmacological Reports 68*, 1266–1275.
Ji, Y. T., Liu, Y. N., & Liu, Z. P. (2015). Tubulin colchicine binding site inhibitors as vascular disrupting agents in clinical developments. *Current Medicinal Chemistry 22*, 1348–1360.
Jiang, J., Mohan, N., Endo, Y., Shen, Y., & Wu, W. J. (2018). Type IIB DNA topoisomerase is downregulated by trastuzumab and doxorubicin to synergize cardiotoxicity. *Oncotarget 9*, 6095–6108.
Jones, R. L., & Ewer, M. S. (2006). Cardiac and cardiovascular toxicity of nonanthracycline anticancer drugs. *Expert Review of Anticancer Therapy 6*, 1249–1269.
de Jonge, M. J., van der Gaast, A., Planting, A. S., van Doorn, L., Lems, A., Boot, I., et al. (2005). Phase I and pharmacokinetic study of the dolastatin 10 analogue TZT-1027, given on days 1 and 8 of a 3-week cycle in patients with advanced solid tumors. *Clinical Cancer Research 11*, 3806–3813.
Kanthou, C., & Tozer, G. M. (2007). Tumour targeting by microtubule-depolymerizing vascular disrupting agents. *Expert Opinion on Therapeutic Targets 11*, 1443–1457.
Kanthou, C., & Tozer, G. M. (2009). Microtubule depolymerizing vascular disrupting agents: novel therapeutic agents for oncology and other pathologies. *International Journal of Experimental Pathology 90*, 284–294.
Ke, Q., Bodyak, N., Rigor, D. L., Hurst, N. W., Chaplin, D. J., & Kang, P. M. (2009). Pharmacological inhibition of the hypertensive response to combretastatin A-4 phosphate in rats. *Vascular Pharmacology 51*, 337–343.
Ke, Q., Samad, M. A., Bae, S., Chaplin, D. J., & Kang, P. M. (2015). Exaggerated hypertensive response to combretastatin A-4 phosphate in hypertensive rats: Effective pharmacological inhibition by diltiazem. *Vascular Pharmacology 74*, 73–79.
Khiati, S., Dalla Rosa, I., Sourbier, C., Ma, X., Rao, V. A., Neckers, L. M., et al. (2014). Mitochondrial topoisomerase I (Top1mt) is a novel limiting factor of doxorubicin cardiotoxicity. *Clinical Cancer Research 20*, 4873–4881.
Kim, L. J., Chamberlain, M. C., Zhu, J., Raizer, J. J., Grimm, S. A., Phuphanich, S., et al. (2011). Phase II study of verubulin (MPC-6827) for the treatment of subjects with recurrent glioblastoma naive to treatment with bevacizumab. *Journal of Clinical Oncology 29*.
Kim, S., Peshkin, L., & Mitchison, T. J. (2012). Vascular disrupting agent drug classes differ in effects on the cytoskeleton. *PLoS One 7*, e40177.
Kridis, W. B., Khanfir, A., Triki, F., & Frikha, M. (2013). An exceptional case of atrial fibrillation arrhythmia induced by etoposide. *Current Drug Safety 8*, 287–289.
Kucharz, J., Michalowska-Kaczmarczyk, A., Zygulska, A. L., Wojtak, J., Pawlik, W., Herman, R. M., et al. (2016). Bradycardia as a rare symptom of cisplatin cardiotoxicity: A case report. *Oncology Letters 11*, 2297–2299.
Ky, B., Vejpongsa, P., Yeh, E. T., Force, T., & Moslehi, J. J. (2013). Emerging paradigms in cardiomyopathies associated with cancer therapies. *Circulation Research 113*, 754–764.
Libutti, S. K., Anthony, L. B., Chaplin, D. J., & Sosa, J. A. (2017). A phase II study of combretastatin A4-phosphate (CA4P) in the treatment of welldifferentiated, low-to intermediate-grade, unresectable, recurrent, or metastatic pancreatic, or GI neuroendocrine tumors/carcinoid (GI-NETs/PNETs) with elevated biomarkers. *Journal of Clinical Oncology 35*, 432.
Lickliter, J., Fida, R., Wheeler, H., Kichenadasse, G., Yang, Q., Ganju, V., et al. (2010). Carboplatin combined with the vascular-disrupting agent CYT997 for recurrent glioblastoma multiforme. *Journal of Clinical Oncology 28*, e13591-e13591.
Lickliter, J., Francesconi, A., Smith, G., Burge, M., Coulthard, A., Rose, S., et al. (2008). Phase I evaluation of CYT997, a novel cytotoxic and vascular-disrupting agent, in patients with advanced cancer. *Journal of Clinical Oncology 26*, 3504.
Lindemann, K., Beale, P. J., Rossi, E., Goh, J. C., Vaughan, M. M., Tenney, M. E., et al. (2019). Phase I study of BNC105P, carboplatin and gemcitabine in partially platinum-sensitive ovarian cancer patients in first or second relapse (ANZGOG-1103). *Cancer Chemotherapy and Pharmacology 83*, 97–105.
Lippert, J. W., III (2007). Vascular disrupting agents. *Bioorganic & Medicinal Chemistry 15*, 605–615.
Lipshultz, S. E., Cochran, T. R., Franco, V. I., & Miller, T. L. (2013). Treatment-related cardiotoxicity in survivors of childhood cancer. *Nature Reviews. Clinical Oncology 10*, 697–710.
Lipshultz, S. E., Lipsitz, S. R., Sallan, S. E., Dalton, V. M., Mone, S. M., Gelber, R. D., et al. (2005). Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology 23*, 2629–2636.
Liu, P., Qin, Y., Wu, L., Yang, S., Li, N., Wang, H., et al. (2014). A phase I clinical trial assessing the safety and tolerability of combretastatin A4 phosphate injections. *Anti-Cancer Drugs 25*, 462–471.
LoRusso, P., Yee, L., Papadopoulos, K. P., Tolcher, A. W., Romero, O., Wang, D., et al. (2007). Phase 1 clinical trials of NPI-2358 (a novel vascular disrupting agent) in patients with solid tumors and lymphomas. *Molecular Cancer Therapeutics 6*, B14.
LoRusso, P. M., Gadgeel, S. M., Wozniak, A., Barge, A. J., Jones, H. K., DelProposto, Z. S., et al. (2008). Phase I clinical evaluation of ZD6126, a novel vascular-targeting agent, in patients with solid tumors. *Investigational New Drugs 26*, 159–167.
Lotrionte, M., Biondi-Zoccai, G., Abbate, A., Lanzetta, G., D'Ascenzo, F., Malavasi, V., et al. (2013). Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *The American Journal of Cardiology 112*, 1980–1984.
Ma, T., Fuld, A. D., Rigas, J. R., Hagey, A. E., Gordon, G. B., Dmitrovsky, E., et al. (2012). A phase I trial and in vitro studies combining ABT-751 with carboplatin in previously treated non-small cell lung cancer patients. *Chemotherapy 58*, 321–329.
Mahal, K., Biersack, B., Caysa, H., Schobert, R., & Mueller, T. (2015). Combretastatin A-4 derived imidazoles show cytotoxic, antivascular, and antimetastatic effects based on cytoskeletal reorganisation. *Investigational New Drugs 33*, 541–554.
Mainwaring, P. N., Lickliter, J., Brown, M. P., Millward, M., Chaplin, D. J., & Goldberg, Z. (2010). A multicenter, open-label phase Ib/II study to assess the safety and clinical activity of intravenous combretastatin A1 diphosphate (OXi4503) as monotherapy in subjects with primary or secondary hepatic tumor burden. *Journal of Clinical Oncology 28*.
Martinelli, M., Bonezzi, K., Riccardi, E., Kuhn, E., Frapolli, R., Zucchetti, M., et al. (2007). Sequence dependent antitumour efficacy of the vascular disrupting agent ZD6126 in combination with paclitaxel. *British Journal of Cancer 97*, 888–894.
Martino, E., Casamassima, G., Castiglione, S., Cellupica, E., Pantalone, S., Papagni, F., et al. (2018). Vinca alkaloids and analogues as anti-cancer agents: Looking back, peering ahead. *Bioorganic & Medicinal Chemistry Letters 28*, 2816–2826.
Martino, E., Della Volpe, S., Terribile, E., Benetti, E., Sakaj, M., Centamore, A., et al. (2017). The long story of camptothecin: From traditional medicine to drugs. *Bioorganic & Medicinal Chemistry Letters 27*, 701–707.
Mason, R. P., Zhao, D., Liu, L., Trawick, M. L., & Pinney, K. G. (2011). A perspective on vascular disrupting agents that interact with tubulin: Preclinical tumor imaging and biological assessment. *Integr Biol (Camb) 3*, 375–387.
Mauer, A. M., Cohen, E. E., Ma, P. C., Kozloff, M. F., Schwartzberg, L., Coates, A. I., et al. (2008). A phase II study of ABT-751 in patients with advanced non-small cell lung cancer. *Journal of Thoracic Oncology 3*, 631–636.
Meinardi, M. T., Gietema, J. A., van der Graaf, W. T., van Veldhuisen, D. J., Runne, M. A., Sluiter, W. J., et al. (2000). Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *Journal of Clinical Oncology 18*, 1725–1732.
Michels, J., Ellard, S. L., Le, L., Kollmannsberger, C., Murray, N., Tomlinson Guns, E. S., et al. (2010). A phase IB study of ABT-751 in combination with docetaxel in patients with advanced castration-resistant prostate cancer. *Annals of Oncology 21*, 305–311.

Millward, M., Mainwaring, P., Mita, A., Federico, K., Lloyd, G. K., Reddinger, N., et al. (2012). Phase 1 study of the novel vascular disrupting agent plinabulin (NPI-2358) and docetaxel. *Investigational New Drugs 30*, 1065–1073.

Millward, M., Mita, A., Spear, M. A., Federico, K. C., Lloyd, G. K., Cropp, G., et al. (2009). Phase I trial of NPI-2358 (a novel vascular disrupting agent) plus docetaxel. *Journal of Clinical Oncology*, 27.

Minchinton, A. I., & Tannock, I. F. (2006). Drug penetration in solid tumours. *Nature Reviews. Cancer 6*, 583–592.

Minotti, G., Saponiero, A., Licata, S., Menna, P., Calafiore, A. M., Teodori, G., et al. (2001). Paclitaxel and docetaxel enhance the metabolism of doxorubicin to toxic species in human myocardium. *Clinical Cancer Research 7*, 1511–1515.

Missiaen, R., Mazzone, M., & Bergers, G. (2018). The reciprocal function and regulation of tumor vessels and immune cells offers new therapeutic opportunities in cancer. *Seminars in Cancer Biology 52*, 107–116.

Mita, M. M., Sargsyan, L., Mita, A. C., & Spear, M. (2013). Vascular-disrupting agents in oncology. *Expert Opinion on Investigational Drugs 22*, 317–328.

Mita, M. M., Spear, M. A., Yee, L. K., Mita, A. C., Heath, E. I., Papadopoulos, K. P., et al. (2010). Phase 1 first-in-human trial of the vascular disrupting agent plinabulin (NPI-2358) in patients with solid tumors or lymphomas. *Clinical Cancer Research 16*, 5892–5899.

Miya, T., Fujikawa, R., Fukushima, J., Nogami, H., Koshiishi, Y., & Goya, T. (1998). Bradycardia induced by irinotecan: a case report. *Japanese Journal of Clinical Oncology 28*, 709–711.

Monk, B. J., Herzog, T., Alvarez, R., Chan, J., Chase, D., Couchenour, R., et al. (2016). FOCUS STUDY: Physician's Choice Chemotherapy (PCC) plus bevacizumab and CA4P versus PCC plus bevacizumab and placebo in platinum-resistant ovarian cancer. *International Journal of Gynecological Cancer 26*, 878–879.

Morgan, R. D., Jayson, G. C., Banerjee, S., Clamp, A. R., Lyon, A. R., Ryder, W. D., et al. (2018). A phase Ib and randomised phase II trial of pazopanib with or without fosbretabulin in advanced recurrent ovarian cancer. *Annals of Oncology 29*, 342.

Murakami, H., Kurata, T., Onozawa, Y., Watanabe, J., Ono, A., Takahashi, T., et al. (2014). An open-label, dose-escalation, safety, and pharmacokinetics phase I study of ombrabulin, a vascular disrupting agent, administered as a 30-min intravenous infusion every 3 weeks in Japanese patients with advanced solid tumors. *Cancer Chemotherapy and Pharmacology 73*, 623–630.

Nathan, P., Zweifel, M., Padhani, A. R., Koh, D. M., Ng, M., Collins, D. J., et al. (2012). Phase I trial of combretastatin A4 phosphate (CA4P) in combination with bevacizumab in patients with advanced cancer. *Clinical Cancer Research 18*, 3428–3439.

Nguyen, L., Fifis, T., & Christophi, C. (2016). Vascular disruptive agent OXi4503 and antiangiogenic agent Sunitinib combination treatment prolong survival of mice with CRC liver metastasis. *BMC Cancer 16*, 533.

Nishio, M., Satouchi, M., Horiike, A., Horio, Y., Sunaga, Y., Ecstein-Fraisse, E., et al. (2018). Phase 1 study of ombrabulin in combination with docetaxel and cisplatin in Japanese patients with advanced solid tumors. *Japanese Journal of Clinical Oncology 48*, 322–328.

Nitiss, J. L. (2009). Targeting DNA topoisomerase II in cancer chemotherapy. *Nature Reviews. Cancer 9*, 338–350.

Nowak, A. K., Brown, C., Millward, M. J., Creaney, J., Byrne, M. J., Hughes, B., et al. (2013). A phase II clinical trial of the vascular disrupting agent BNC105P as second line chemotherapy for advanced Malignant Pleural Mesothelioma. *Lung Cancer 81*, 422–427.

Octavia, Y., Tocchetti, C. G., Gabrielson, K. L., Janssens, S., Crijns, H. J., & Moens, A. L. (2012). Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. *Journal of Molecular and Cellular Cardiology 52*, 1213–1225.

Oh, D. Y., Kim, T. M., Han, S. W., Shin, D. Y., Lee, Y. G., Lee, K. W., et al. (2016). Phase I study of CKD-516, a novel vascular disrupting agent, in patients with advanced solid tumors. *Cancer Research and Treatment 48*, 28–36.

Oun, R., & Rowan, E. (2017). Cisplatin induced arrhythmia; electrolyte imbalance or disturbance of the SA node? *European Journal of Pharmacology 811*, 125–128.

Pal, S., Azad, A., Bhatia, S., Drabkin, H., Costello, B., Sarantopoulos, J., et al. (2015). A phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma. *Clinical Cancer Research 21*, 3420–3427.

Pasquier, E., Tuset, M. P., Street, J., Sinnappan, S., MacKenzie, K. L., Braguer, D., et al. (2013). Concentration- and schedule-dependent effects of chemotherapy on the angiogenic potential and drug sensitivity of vascular endothelial cells. *Angiogenesis 16*, 373–386.

Patane, S. (2014). Cardiotoxicity: Cisplatin and long-term cancer survivors. *International Journal of Cardiology 175*, 201–202.

Patel, S., Keohan, M. L., Saif, M. W., Rushing, D., Baez, L., Feit, K., et al. (2006). Phase II study of intravenous TZT-1027 in patients with advanced or metastatic soft-tissue sarcomas with prior exposure to anthracycline-based chemotherapy. *Cancer 107*, 2881–2887.

Patterson, D. M., Ross, P., Koetz, B., Saleem, A., Stratford, M., Stirling, J., et al. (2007). Phase I evaluation of OXi4503, a vascular disrupting agent, in patients with advanced solid tumours. *Journal of Clinical Oncology*, 25.

Patterson, D. M., Zweifel, M., Middleton, M. R., Price, P. M., Folkes, L. K., Stratford, M. R., et al. (2012). Phase I clinical and pharmacokinetic evaluation of the vascular-disrupting agent OXi4503 in patients with advanced solid tumors. *Clinical Cancer Research 18*, 1415–1425.

von Pawel, J., Gorbounova, V., Reck, M., Kowalski, D. M., Allard, A., Chadjaa, M., et al. (2014). DISRUPT: A randomised phase 2 trial of ombrabulin (AVE8062) plus a taxane-platinum regimen as first-line therapy for metastatic non-small cell lung cancer. *Lung Cancer 85*, 224–229.

Pendleton, M., Lindsey, R. H., Jr., Felix, C. A., Grimwade, D., & Osheroff, N. (2014). Topoisomerase II and leukemia. Annals of the New York Academy of Sciences, 1310, 98-110.

Piegari, E., De Angelis, A., Cappetta, D., Russo, R., Esposito, G., Costantino, S., et al. (2013). Doxorubicin induces senescence and impairs function of human cardiac progenitor cells. *Basic Research in Cardiology 108*, 334.

Polk, A., Vaage-Nilsen, M., Vistisen, K., & Nielsen, D. L. (2013). Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treatment Reviews 39*, 974–984.

Pommier, Y. (2013). Drugging topoisomerases: lessons and challenges. *ACS Chemical Biology 8*, 82–95.

Raschi, E., Vasina, V., Ursino, M. G., Boriani, G., Martoni, A., & De Ponti, F. (2010). Anticancer drugs and cardiotoxicity: Insights and perspectives in the era of targeted therapy. *Pharmacology & Therapeutics 125*, 196–218.

Renu, K., Abilash, V. G., Tirupathi, P. P. B., & Arunachalam, S. (2018). Molecular mechanism of doxorubicin-induced cardiomyopathy - An update. *European Journal of Pharmacology 818*, 241–253.

Reyes-Aldasoro, C. C., Wilson, I., Prise, V. E., Barber, P. R., Ameer-Beg, M., Vojnovic, B., et al. (2008). Estimation of apparent tumor vascular permeability from multiphoton fluorescence microscopic images of P22 rat sarcomas in vivo. *Microcirculation 15*, 65–79.

Rhea, I. B., & Oliveira, G. H. (2018). Cardiotoxicity of novel targeted chemotherapeutic agents. *Current Treatment Options in Cardiovascular Medicine 20*, 53.

Ricart, A. D., Ashton, E. A., Cooney, M. M., Sarantopoulos, J., Brell, J. M., Feldman, M. A., et al. (2011). A phase I study of MN-029 (denibulin), a novel vascular-disrupting agent, in patients with advanced solid tumors. *Cancer Chemotherapy and Pharmacology 68*, 959–970.

Riely, G. J., Gadgeel, S., Rothman, I., Saidman, B., Sabbath, K., Feit, K., et al. (2007). A phase 2 study of TZT-1027, administered weekly to patients with advanced non-small cell lung cancer following treatment with platinum-based chemotherapy. *Lung Cancer 55*, 181–185.

Rischin, D., Bibby, D. C., Chong, G., Kremmidiotis, G., Leske, A. F., Matthews, C. A., et al. (2011). Clinical, pharmacodynamic, and pharmacokinetic evaluation of BNC105P: a phase I trial of a novel vascular disrupting agent and inhibitor of cancer cell proliferation. *Clinical Cancer Research 17*, 5152–5160.

Rowinsky, E. K., McGuire, W. P., Guarnieri, T., Fisherman, J. S., Christian, M. C., & Donehower, R. C. (1991). Cardiac disturbances during the administration of taxol. *Journal of Clinical Oncology 9*, 1704–1712.

Rudek, M. A., Dasari, A., Laheru, D., He, P., Jin, R., Walker, R., et al. (2016). Phase 1 study of ABT-751 in combination with CAPIRI (Capecitabine and Irinotecan) and bevacizumab in patients with advanced colorectal cancer. *Journal of Clinical Pharmacology 56*, 966–973.

Rudin, C. M., Mauer, A., Smakal, M., Juergens, R., Spelda, S., Wertheim, M., et al. (2011). Phase I/II study of pemetrexed with or without ABT-751 in advanced or metastatic non-small-cell lung cancer. *Journal of Clinical Oncology 29*, 1075–1082.

Rustin, G. J., Galbraith, S. M., Anderson, H., Stratford, M., Folkes, L. K., Sena, L., et al. (2003). Phase I clinical trial of weekly combretastatin A4 phosphate: Clinical and pharmacokinetic results. *Journal of Clinical Oncology 21*, 2815–2822.

Rustin, G. J., Shreeves, G., Nathan, P. D., Gaya, A., Ganesan, T. S., Wang, D., et al. (2010). A Phase Ib trial of CA4P (combretastatin A-4 phosphate), carboplatin, and paclitaxel in patients with advanced cancer. *British Journal of Cancer 102*, 1355–1360.

Salvatorelli, E., Menna, P., Cantalupo, E., Chello, M., Covino, E., Wolf, F. I., et al. (2015). The concomitant management of cancer therapy and cardiac therapy. *Biochimica et Biophysica Acta 1848*, 2727–2737.

Schwartz, E. L. (2009). Antivascular actions of microtubule-binding drugs. *Clinical Cancer Research 15*, 2594–2601.

Schwarzer, S., Eber, B., Greinix, H., & Lind, P. (1991). Non-Q-wave myocardial infarction associated with bleomycin and etoposide chemotherapy. *European Heart Journal 12*, 748–750.

Sessa, C., Lorusso, P., Tolcher, A., Farace, F., Lassau, N., Delmonte, A., et al. (2013). Phase I safety, pharmacokinetic and pharmacodynamic evaluation of the vascular disrupting agent ombrabulin (AVE8062) in patients with advanced solid tumors. *Clinical Cancer Research 19*, 4832–4842.

Sessa, C., & Pagani, O. (2001). Docetaxel and epirubicin in advanced breast cancer. *Oncologist 6*(Suppl. 3), 13–16.

Shahi, P. K., & Pineda, I. F. (2008). Tumoral angiogenesis: Review of the literature. *Cancer Investigation 26*, 104–108.

Sharma, P., & Allison, J. P. (2015a). The future of immune checkpoint therapy. *Science 348*, 56–61.

Sharma, P., & Allison, J. P. (2015b). Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. *Cell 161*, 205–214.

Siemann, D. W. (2011). The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by tumor-vascular disrupting agents. *Cancer Treatment Reviews 37*, 63–74.

Siemann, D. W., Chaplin, D. J., & Horsman, M. R. (2017). Realizing the potential of vascular targeted therapy: The rationale for combining vascular disrupting agents and antiangiogenic agents to treat cancer. *Cancer Investigation 35*, 519–534.

Siemann, D. W., Chaplin, D. J., & Walicke, P. A. (2009). A review and update of the current status of the vasculature-disabling agent combretastatin-A4 phosphate (CA4P). *Expert Opinion on Investigational Drugs 18*, 189–197.

Song, W., Tang, Z., Zhang, D., Wen, X., Lv, S., Liu, Z., et al. (2016). Solid tumor therapy using a cannon and pawn combination strategy. *Theranostics 6*, 1023–1030.

Sosa, J. A., Elisei, R., Jarzab, B., Bal, C. S., Koussis, H., Gramza, A. W., et al. (2011). A randomized phase II/III trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C) and paclitaxel (P) in anaplastic thyroid cancer (ATC): Final survival analysis for the FACT trial. *Journal of Clinical Oncology 29*, 5502.

Sosa, J. A., Elisei, R., Jarzab, B., Balkissoon, J., Lu, S. P., Bal, C., et al. (2014). Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. *Thyroid 24*, 232–240.

Subbiah, I. M., Lenihan, D. J., & Tsimberidou, A. M. (2011). Cardiovascular toxicity profiles of vascular-disrupting agents. *Oncologist 16*, 1120–1130.

Takahashi, S., Nakano, K., Yokota, T., Shitara, K., Muro, K., Sunaga, Y., et al. (2016). Phase 1 study of ombrabulin in combination with cisplatin (CDDP) in Japanese patients with advanced solid tumors. *Japanese Journal of Clinical Oncology 46*, 1000–1007.

Tamura, K., Nakagawa, K., Kurata, T., Satoh, T., Nogami, T., Takeda, K., et al. (2007). Phase I study of TZT-1027, a novel synthetic dolastatin 10 derivative and inhibitor of tubulin polymerization, which was administered to patients with advanced solid tumors on days 1 and 8 in 3-week courses. *Cancer Chemotherapy and Pharmacology 60*, 285–293.

Tocchetti, C. G., Gallucci, G., Coppola, C., Piscopo, G., Cipresso, C., Maurea, C., et al. (2013). The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors. *European Journal of Heart Failure 15*, 482–489.

Tochinai, R., Nagata, Y., Ando, M., Hata, C., Suzuki, T., Asakawa, N., et al. (2016). Combretastatin A4 disodium phosphate-induced myocardial injury. *Journal of Toxicologic Pathology 29*, 163–171.

Todaro, M. C., Oreto, L., Qamar, R., Paterick, T. E., Carerj, S., & Khandheria, B. K. (2013). Cardioncology: State of the heart. *International Journal of Cardiology 168*, 680–687.

Todd, A. A., Groundwater, P. W., & Gill, J. (2017). *Anticancer therapeutics: From drug discovery to clinical applications* (1st ed.). Hoboken, NJ: Wiley.

Touyz, R. M., Herrmann, S. M. S., & Herrmann, J. (2018). Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. *Journal of the American Society of Hypertension 12*, 409–425.

Tozer, G. M., Akerman, S., Cross, N. A., Barber, P. R., Bjorndahl, M. A., Greco, O., et al. (2008). Blood vessel maturation and response to vascular-disrupting therapy in single vascular endothelial growth factor-A isoform-producing tumors. *Cancer Research 68*, 2301–2311.

Tozer, G. M., Kanthou, C., & Baguley, B. C. (2005). Disrupting tumour blood vessels. *Nature Reviews. Cancer 5*, 423–435.

Traynor, A. M., Gordon, M. S., Alberti, D., Mendelson, D. S., Munsey, M. S., Wilding, G., et al. (2010). A dose escalation, safety, and tolerability study of MN-029 in patients with advanced solid tumors. *Investigational New Drugs 28*, 509–515.

Turner, D., Gonzalez, A., Pettiford, L., Meacham, A., Wise, E., Bosse, R. C., et al. (2013). A phase I study of the vascular disrupting combretastatin, OXi4503, in patients with relapsed and refractory Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS). *Blood*, 122.

Varricchi, G., Galdiero, M. R., Marone, G., Criscuolo, G., Triassi, M., Bonaduce, D., et al. (2017). Cardiotoxicity of immune checkpoint inhibitors. *ESMO Open 2*, e000247.

Varricchi, G., Galdiero, M. R., & Tocchetti, C. G. (2017). Cardiac toxicity of immune checkpoint inhibitors: Cardio-oncology meets immunology. *Circulation 136*, 1989–1992.

Vasiliadis, I., Kolovou, G., & Mikhailidis, D. P. (2014). Cardiotoxicity and cancer therapy. *Angiology 65*, 369–371.

Vejpongsa, P., & Yeh, E. T. (2014). Topoisomerase 2beta: A promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clinical Pharmacology and Therapeutics 95*, 45–52.

Watts, J. M., Swords, R. T., Cogle, C. R., Schiller, G. J., & Lin, T. L. (2017). Results from a phase 1b (OX1222) dose-ranging study of OXi4503 combined with cytarabine in patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome. *Blood*, 130.

Weinstein, I. B., & Joe, A. K. (2006). Mechanisms of disease: Oncogene addiction–a rationale for molecular targeting in cancer therapy. *Nature Clinical Practice. Oncology 3*, 448–457.

Weis, S. M., & Cheresh, D. A. (2011). Tumor angiogenesis: Molecular pathways and therapeutic targets. *Nature Medicine 17*, 1359–1370.

Yamamoto, N., Andoh, M., Kawahara, M., Fukuoka, M., & Niitani, H. (2009). Phase I study of TZT-1027, a novel synthetic dolastatin 10 derivative and inhibitor of tubulin polymerization, given weekly to advanced solid tumor patients for 3 weeks. *Cancer Science 100*, 316–321.

Yano, S., & Shimada, K. (1996). Vasospastic angina after chemotherapy by with carboplatin and etoposide in a patient with lung cancer. *Japanese Circulation Journal 60*, 185–188.

Yee, K. W., Hagey, A., Verstovsek, S., Cortes, J., Garcia-Manero, G., O'Brien, S. M., et al. (2005). Phase 1 study of ABT-751, a novel microtubule inhibitor, in patients with refractory hematologic malignancies. *Clinical Cancer Research 11*, 6615–6624.

Yeh, E. T. (2006). Cardiotoxicity induced by chemotherapy and antibody therapy. *Annual Review of Medicine 57*, 485–498.

Yeh, E. T., & Bickford, C. L. (2009). Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *Journal of the American College of Cardiology 53*, 2231–2247.

Zhu, J. J., Recht, L. D., Colman, H., Kesari, S., Kim, L. J., Balch, A. H., et al. (2011). Phase Ii study using the response assessment in neuro-oncology (Rano) criteria to evaluate the efficacy of verubulin with radiation therapy and temozolomide in subjects newly diagnosed with glioblastoma multiforme: Part a safety and tolerability results. *Neuro-Oncology 13*, 86–87.

Zweifel, M., Jayson, G. C., Reed, N. S., Osborne, R., Hassan, B., Ledermann, J., et al. (2011). Phase II trial of combretastatin A4 phosphate, carboplatin, and paclitaxel in patients with platinum-resistant ovarian cancer. *Annals of Oncology 22*, 2036–2041.