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Towards the Use of Localised Delivery Strategies to Counteract Cancer Therapy Induced Cardiotoxicities

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Abstract

Cancer therapies have significantly improved cancer survival; however, these therapies can often result in undesired side effects to off target organs. Cardiac disease ranging from mild hypertension to heart failure can occur as a result of cancer therapies. This can warrant the discontinuation of cancer treatment in patients which can be detrimental, especially when the treatment is effective. There is an urgent need to mitigate cardiac disease that occurs as a result of cancer therapy. Delivery strategies such as the use of nanoparticles, hydrogels, and medical devices can be used to localise the treatment to the tumour and prevent off target side effects. This review summarises the advancements in localised delivery of anti-cancer therapies to tumours. It also examines the localised delivery of cardioprotectants to the heart for patients with systemic disease such as leukaemia where localised tumour delivery might not be an option.

Graphical Abstract

Keywords

Cancer therapy, localised drug delivery, cardiotoxicity, Immune checkpoint inhibitors, myocarditis, cardioprotectant.

Introduction

Cancer is a major healthcare problem globally and is one of the leading causes of death worldwide (1). It is the second most common cause of death in the USA (2). GLOBOCAN estimates 18.1 million new cases and 9.6 million cancer deaths worldwide in the year 2018 (1). As per the projection for 2020, 1,806,590 new cancer cases and 606,520 cancer deaths will occur in the USA alone (3). Over the past few years, there has been a decrease in overall cancer related mortality. For example, in USA, the combined cancer death rate for both men and women dropped continuously through 2017 by a total of 29%, that is, approximately 2.9 million less cancer deaths than expected (3). No doubt, advancements in chemotherapeutics have played a major role in reducing the cancer death rate that has seen a decline over the past decade.

Although cancer therapies are successful in the treatment of cancer, their use often results in undesired side effects, most notably, cardiotoxicity which could lead to various cardiac diseases demonstrated in Figure 1. This could be detrimental to the patient's treatment and can result in the discontinuation of cancer therapy. Several subclasses of cancer therapies result in the formation of cardiac disease including the use of anthracyclines, targeted therapies such as anti-HER2 treatment and vascular endothelial growth factor (VEGF) receptor inhibitors, and most recently noted immune checkpoint inhibitors (ICIs). These cardiovascular diseases can range from hypertension to severe cardiomyopathies resulting in congestive heart failure (CHF) which has excellently been reviewed in detail elsewhere (4). Such therapies can be broadly characterised into causing vascular damage, cardiomyopathy, arrythmia, and pericardial disease as outlined in Figure 1. There is thus an unmet need to overcome off target side effects of these cancer therapies. This paper discusses the problem of cardiac disease from these therapies and potential strategies to overcome these off-target effects, including strategies for localised delivery of chemotherapeutics to the tumour site and localised cardioprotectant delivery to the heart for systemic malignancies, for example, haematological malignancies for which localised anti-tumour treatment is not an option.

Fig. 1 Outline of anti-cancer agents resulting in toxicities related to vascular changes, cardiomyopathy, pericardial disease, and arrhythmia

Agents Causing Cancer Therapy Induced Cardiotoxicities

Cancer therapy induced cardiotoxicity is a generalised term for a group of cardiac diseases resulting from treatment with either traditional cancer therapeutics such as chemotherapies and radiotherapies or novel targeted therapies such as monoclonal antibody therapies. The diseases can manifest in several different ways which is depending on the therapeutic strategy used including myocardial, pericardial, and vascular diseases (5). This may lead to left ventricular dysfunction resulting in a reduced left ventricular ejection fraction (LVEF) and CHF.

Anthracyclines

Anthracyclines are the most commonly used chemotherapeutic agents. Despite their remarkably known curative effect, their use is limited because of the adverse effect on the heart. Anthracyclines often induce irreversible degenerative cardiomyopathy which leads to CHF with time and is fatal (6). Chemotherapy induced cardiotoxicity leading to CHF has been associated with a 3.5 fold increased mortality risk as compared to the CHF caused by the idiopathic cardiomyopathy (7). The mortality rate can be as high as up to 60% at 2 years post treatment (8). Anthracyclines can result in an acute or chronic cardiotoxicity and while most patients may be exposed to the initial acute cardiotoxicity, patients who receive high doses or are treated early in life may be more exposed to the late onset side effects of anthracyclines including CHF. Over 50% of the greater than 330,000 childhood cancer survivors in the USA have been treated with anthracyclines (9). Although they have significantly improved survival by >75% they are associated with the development of chronic cardiotoxicity causing lifelong problems with childhood survivors of cancer treatment being particularly vulnerable (10,11).

There are several suggestions on possible mechanisms of action although it is widely accepted that the formation of reactive oxygen species, lipid peroxidation of the cell membrane, and mitochondrial dysfunction play a role which ultimately damage the cardiomyocyte leading to irreversible heart damage (12,13). The incidence of left ventricular dysfunction associated with anthracycline therapy can vary depending on the type of drug used but it is generally dose dependent. Doxorubicin is one of the most commonly used anthracyclines containing a dose dependent increase with rates of up to 5%, 26% and 48% with 400mg/m^2, 550mg/m^2, and 700mg/m^2 respectively (14). Other types of anthracyclines can be associated with cardiotoxicity such as idarubicin (>90mg/m2), epirubicin (>900mg/m2), and mitoxanthone (>120mg/m) which have reported incidences of up to 18%, 11.4% and 2.6% respectively (5). Due to this high rate of reported cardiotoxicity, there is a need to develop localised delivery strategies that either deliver the drug directly to the tumour resulting in reduction in off target side effects or development of delivery strategies that deliver therapeutics to the heart to prevent cardiotoxicity.

Targeted Therapies

Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitor

Human epidermal growth factor receptor 2 (HER2) inhibition using trastuzumab has been shown to be effective by increasing overall survival and disease free survival, however, this has been associated with significantly increased levels of CHF and LVEF decline (15). The rate of cardiac dysfunction has been reported to lie between 7% and 34% in patients receiving a combination of anthracyclines and trastuzumab (5,15). Additionally, the use of trastuzumab in combination with antimetabolites and alkalising agents were associated with cardiac dysfunction and CHF at rates of 5% and <1% in patients with gastric cancers (5,16). However, trastuzumab is only involved in acute toxicity and not in chronic toxicities. Several studies have followed patients receiving trastuzumab for up to ten years and these studies have concluded that trastuzumab has a low risk of cardiac events and have found the improvements in overall survival and disease-free survival. The positive effects of trastuzumab outweighs the potential benefits of any acute side effects (17–21). It occurs around the time of treatment and thus is more reversible. This is thought to be due to the mechanism of action of these agents that result in structural and functional changes in both the

mitochondria and the contractile proteins which rarely leads to cell death. This is a possible explanation as to why trastuzumab therapy is reversible and is not associated with long term effects as opposed to the use of agents such as anthracyclines which result in cardiomyocyte death (5,22,23). Other anti-HER2 pathway targeted therapies such as lapatinib, pertuzumab, and trastuzumab-emtansine seem to show similar results to trastuzumab although larger prospective trials may be needed for confirmation (5,24,25). A study comparing the use of trastuzumab vs trastuzumab and lapatinib in over 8000 patients with breast cancer has shown no improvement in disease free survival and low rates of cardiotoxicity in both groups (5,26).

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Blocking the VEGF pathway has shown promising results in several solid cancers; however, they are often associated with both reversable and irreversible cardiac side effects. A large metanalysis of Food and Drug Administration (FDA) approved VEGF receptor TKIs containing 10,647 patients from 21 randomised phase II and III clinical trials examined the risk of CHF associated with the drugs. This study found a 2.69 fold increase in CHF risk compared to controls not using TKIs which was deemed significant (5,27). However, this study also found there was no significant increase in the risk of severe CHF between the groups (27). A trial examining the effects of the anti-VEGF antibody bevacizumab after chemotherapy resulted in development of left ventricular dysfunction in 2% of patients and resulted in severe CHF in 2% of patients (5,28). A comparison of the VEGF inhibitors pazopanib and sunitinib has shown that both have similar efficacy and although there was no difference between the two in cardiovascular events the data favoured pazopanib in safety and quality of life profiles (29). The use of the VEGF inhibitors pazopanib, sunitinib, and axitinib has shown that their use is associated with rates of cardiac dysfunction between 3-15% and between 1-10% of patients will develop CHF (5,30–32). VEGF inhibitors have also been found to result in arterial hypertension which can lead to cardiac dysfunction. If cardiac dysfunction does develop, it can be reversible in 60-80% of patients upon treatment discontinuation (33). Additionally, it can also be suggested that if hypertension is controlled, the potential of CHF may be reduced (5,34).

Immune Checkpoint Inhibitors (ICI)

Recently approved by the FDA, ICIs have emerged as a promising anti-cancer treatment option and has been increasingly used in earlier stages of the disease (35). Tumour cells, by various molecular pathways, suppress the activation of adaptive and innate immune systems that may poise threat to them. Leach DR *et al* in their landmark study observed the rejection of tumours in a murine model when antibodies against cytotoxic T lymphocyte antigen 4 (CTLA-4) were introduced (36). Hence, it was inferred that blocking the inhibitory regulation could unleash the immune system against the tumour cells and that is the basis of the ICI therapy. Although ICIs exploit the potential of the self-immune system to destroy the tumour cells, the up-regulation of the immune system is also associated with immune-mediated adverse events (imAEs). Any human body system can be affected by an imAEs. It is reported that these imAEs lead to the discontinuation of the ICI therapy in approximately 40% of the patients (37,38) . Cardiovascular imAEs occurring as a result of ICI therapy are often severe and life threating. Salem *et al* have reported that >80% of cardiovascular imAEs are severe with death occurring in 50% of myocarditis cases and 21% of pericardial diseases. Thus, there exists an urgent need to develop new management strategies and therapeutics to treat cardiovascular imAEs (39).

ICI-induced myocarditis is a fulminant and potentially fatal complication that may warrant discontinuation of the ICI therapy. Sporadic cases of ICI-induced myocarditis have been reported. Though sparsely reported in early trials and considered to be a rare complication occurring in less than 1% of the patients receiving ICI therapy (40), the frequency seems to be increasing. Most recently, Mahmood *et al* created an 8-centre institutional registry to better understand the statistics of ICI-mediated myocarditis. The prevalence of ICI-induced myocarditis was found to be 1.14% in adult patients while the median time of onset was 34 days after starting ICI (41). The majority of patients presented with abnormal electrocardiogram (ECG), elevated troponin and NT-proBNP (N-terminal pro B-type natriuretic peptide) levels and nearly half of the patients had ejection fraction of <50%. Patients were managed with high dose steroids which resulted in lower serum troponin levels at discharge and no case of recurrent myocarditis was reported (41). Major adverse cardiovascular events (MACE) were found to be high in patients with ICI-induced

myocarditis. At a median follow up of 102 days, nearly half of the patients with myocarditis experienced a MACE, including cardiovascular death, cardiogenic shock and cardiac arrest (41). Hence, surveillance and early detection of ICI-induced myocarditis is the key to prevent such serious and potentially fatal complications.

The incidence of cardiotoxicities associated with ICIs, although it appears to be arguably low, seems particularly elevated in patients following a combination therapy regimen (42). With pertinence to ICI-induced cardiotoxicity, a combination therapy is defined as a therapy that employs a concoction of pathways, such as PD-1, CTLA-4 and PDL-1inhibition. In particular, a combination therapy in the context of ICIs refers to the uptake of a dual-drug regimen, often Ipilimumab and Nivolumab. Beyond cardiomyopathy, however, K. Abdallah, et al. also report an increased incidence of varying degrees of heart-block, arrhythmia, and new-onset CHF, all of which can be fatal in a patient undergoing oncological treatment with ICIs (42). While the majority of cardiotoxicity-related cases are seen within the first few months of commencement of therapy, it is imperative to note that cardiac symptoms—such as palpitations, shortness of breath, and irregular heartbeat—often overlap with symptoms such as myositis, which occur due to concomitant organ toxicities, making the diagnosis of cardiotoxicity a considerable challenge.

Although the enthusiasm of using ICI therapy has been extended to the paediatric cancer population to achieve substantial disease response, there is limited data available as it has only been used in some cases. Hence, it is difficult to comment on the long-term safety and efficacy of ICI therapy in this population. In majority of the published cases, the adult dosage of ICI therapy was prescribed in the paediatric population (43). Merchant MS *et al* in their phase I clinical trial used anti CTLA-4 agent, ipilimumab, to treat recurrent or refractory paediatric solid tumours like sarcomas, melanomas, renal/bladder carcinomas and neuroblastoma (44). The trial was designed to evaluate the safety and pharmacokinetics of ipilimumab up to 10 mg/kg. Dose-limiting toxicities were observed at 5 and 10 mg/kg dose levels (44). There are some on-going clinical trials of single and combined ICI therapy in paediatric cancer patients with recurrent or progressive/refractory disease leading to a better understanding of the safety and efficacy profile of ICI therapy in the in paediatric population (43).

Strategies that deliver the therapeutic directly to the tumour have great potential in the ICI induced cardiotoxicity space and could minimise the potential of these therapies to cause cardiotoxicity. However, such strategies may not be applicable to systemic malignancies such as leukaemia. It is also unknown if delivery of steroids will have an effect on patient outcomes, therefore, there also exists an unmet clinical need to deliver prophylactic and therapeutics directly to the heart in order to reduce ICI cardiotoxicity. Such local delivery strategies could incorporate the use of gene therapy, stem cells, and drugs in order to reduce cardiotoxicity related to ICI therapy (45–47).

A Need for Novel Localised Delivery Strategies

Traditional drug delivery strategies are largely focused on drug delivery through oral, intravenous, and transdermal routes for drug delivery which have several limitations (48). Oral strategies are the most common route of drug delivery, however, therapeutics are exposed to the acidic environment in the stomach, the alkaline environment in the intestines, and can have poor absorption in the intestines (48). This makes this route difficult for the delivery of poorly soluble drugs and peptide-based therapeutics. While intravenous delivery can overcome most of these limitations a health care professional is required for administration. Transdermal delivery can be an alternative route but there are limited number of drugs with the ability to pass the epithelial barrier of the epidermis and are only applicable to cancers localised to the upper layers of the skin (48). These limitations have led the use of more sophisticated systems for drug delivery including liposomes, nanoparticles, injectable biomaterials, and microneedle patches as shown in Figure 2.

It is clear that cancer therapies result in off-target side effects, to which, the heart is particularly susceptible leading to life threatening cardiac disease. Due to the off-target side effects that occur as a result of anti-cancer therapies, it is important that delivery strategies are improved in order to prevent such side effects. Two approaches that can be taken for this is either localised delivery directly to the tumour or localised delivery of cardioprotectant to the heart which may mitigate cardiac side effects, especially when localised tumour delivery is not an option. Reducing the

off-target side effects of cancer therapy would increase the tolerability of drugs and allow higher dosages at the target site while mitigating the off-target side effects. There are several other side effects, which can be prevented by such localised delivery such as those that cause discomfort to the patient but do not necessarily warrant the discontinuation of the therapy, such as nausea and hair loss. Novel drug delivery strategies to deliver anti-cancer therapies using targeted and localised approaches will be discussed in detail below and are demonstrated in Figure 2. Also, Table 1 shows the approved therapeutic products for targeted delivery and Table 2 gives the details of the localized strategies for tumour targeting in preclinical studies.

Fig. 2 Localised delivery strategies that can be used to delivery drugs directly to tumours

Anthracyclines

Several strategies have been used in order to localise delivery of anthracyclines to target sites while reducing off target side effects. Liposomal forms of anthracyclines have been used in order to reduce the off-target side effects and enhance therapy with both pegylated and non-pegylated forms of liposomes being approved for use in patients (49). Liposomal forms of doxorubicin have improved overall response rates and reduced the rates of cardiotoxicity (50). The aim of such strategies is for selective accumulation of drug to the tumour site in order to maximise the anti-cancer properties while equally preventing build up in off target sites. The advantage of peglayting liposomes is that they avoid the phagocytic system and have a longer circulating time due to reduced renal clearance in comparison to non-pegylated forms of liposomes (51)..Doxil® was the first liposomal nanoparticle formulation to receive regulatory approval for treatment in AIDS related Kaposi sarcoma, multiple myeloma, and ovarian cancer due to the failure and intolerance of other systemic therapies. Doxil® had a half-life of 45 hours in comparison to 2 hours for free doxorubicin, additionally, Doxil® showed a 4-16 times higher accumulation in the tumour in comparison to doxorubicin and additionally has shown reduced cardiotoxicity in comparison to free doxorubicin

(49,52,53). Since the approval of Doxil®, a pegylated liposome, several other anthracycline liposomal formulations have been approved for use including Myocet® and DaunoXome®. Myocet® is an approved form of non-pegylated liposomal doxorubicin approved for use in combination with cyclophosphamide for treatment in metastatic breast cancers. Myocet® reduces chemotherapy induced cardiotoxicity while maintaining efficacy due to the large size of the vesicles. This minimises exposure to healthy tissues and targets the tumour due to leaky blood vessels (54,55). Phase III clinical trials of Myocet® also showed similar progression free survival and response rates compared to free doxorubicin while also significantly reducing the rates of cardiac events and rates of CHF (56,57). DanuoXome® is a liposomal form of the anthracycline Daunorubicin which has been approved for the use in Kaposi's sarcoma. A phase I/II clinical trial showed that DanuoXome ® showed better pharmokinetic profiles than free daunorubicin with an increased half-life of up to 5.6 hours in comparison to 0.77 hours for daunorubicin. However in this trial there was no significant differences in the rates of cardiotoxicity (58,59). Another phase II clinical trial assessing the efficacy of liposomal DanuoXome® showed reduced rates of pulmonary symptoms and no reported cardiotoxicity in the trial (60). A phase III trial comparing the use of DanuoXome® to a regiment of doxorubicin, bleomycin, and vincristine in Kaposi sarcoma found no significant differences in response rates and no cardiotoxicity in either arm of the study (61).

Due to the leaky blood vessels and poor lymphatic drainage in tumour sites there tends to be a build-up of drug in tumours (53). This has led to the development of nanoparticle formulations with preferential build up in tumour sites, additionally, such particles can be combined with the use of antibodies, peptides, and small molecules in order to target specific surface receptors associated with tumours that are present in smaller amounts in healthy tissues (62). Receptors can then be internalised, and drugs can unleash their drug loads into the cytoplasm of the cells which can increase the cytotoxicity of drugs. A group has worked on the development of a hyperbranched doxorubicin polymer that targets prostate specific membrane antigen which is overexpressed in prostate cancer cells but not on normal prostate cells. This system is also a pH responsive system that has no drug release at neutral pH and rapidly releases drug in response to lower pH of 5.5. This system allows triggered release upon uptake of the particles into

endosomes which targets the cell internally, additionally these hyperbranched polymers were found to have a high uptake in LNCaP prostate cancer cells when coated with an active target ligand for prostate specific membrane antigen. Additionally, the hyperbranched polymer containing the active ligand reduced tumour size compared to the other groups (63).. Furthermore, drug-polymer conjugation is an advanced strategy for localised and targeted drug delivery. One such example is the co-conjugation of doxorubicin and aminoglutethimide to PGA via a pH liable linker in order to target the acidic tumour microenvironment. The polymer conjugation strategy was found to reduce tumour size and reduce lung metastases by 90% in a preclinical metastatic triple-negative breast cancer murine model. Metronomic approaches which involve frequent low dose administration of drugs have been shown to be advantageous (64). Several clinical trials using metronomic approaches breast, prostate, gastrointestinal, renal and pancreatic cancers, and melanoma have been performed (64). However, there are concerns surrounding these approaches including low tumour drug accumulation, effectiveness in chemoresistant and metastatic tumours, and development of chemoresistance with prolonged treatment. Novel drug delivery strategies such as localised and targeted delivery may offer a solution to this problem. For example, Mazzucchelli *et al* have shown the effectiveness of a H-ferritin (HF-n) mediated targeted nano delivery of metronomic doxorubicin. The authors found that metronomic delivery of HF-n-doxorubicin had a potent anti-tumour effect in comparrision to doxorubicin, prevented angiogenesis, and prevented chemoresistance. Furthermore, the approach showed proven avoidance of off target side effects and prevention of cardiotoxicity (64). Exosomes are an emerging strategy used to deliver DNA, RNA, and protein based therapeutics but can also be loaded externally with drugs in order to develop a novel drug delivery solution that allows for enhanced drug uptake. It was shown in both in vitro and in vivo models that when exosomal doxorubicin worked as well as doxorubicin but reduced doxorubicin concentrations in the heart by up to 40%.

Transarterial chemoembolization has been used for use in both primary and metastatic liver cancers; this procedure starves the tumour of oxygen resulting in cell death by blocking of a blood vessel that feeds the tumour. It is currently the gold standard for treatment in hepatocellular carcinomas. These blood vessels can be blocked by using beads which can be effective with or without drug loading of chemotherapeutic agents in order to target the tumour

(65). A study that compared the use of a drug eluting bead (DEB) combined with TACE (DEB-TACE) versus conventional TACE alone found that 11 patients received and complete response in the DEB-TACE group while 6 patients had a complete response in the conventional TACE group. There was also more reoccurrence in the TACE only group with 78.3% versus DEB-TACE 45.7% at 12 months with also a significant difference in the time to progression in DEB-TACE group (36.2 weeks) versus TACE group (42.4 weeks) (66). Such strategies that localise the chemotherapy to the tumour may be beneficial for drug delivery and offsetting cardiotoxicity although further data may be needed to confirm this.

Targeted Therapies

Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors

Research has also been conducted into the localised delivery of therapeutics such as the HER-2 inhibitor trastuzumab. Multiple delivery modalities have been used including the use of hydrogels and microparticles. Subcutaneous delivery of trastuzumab has shown to have similar pharmacokinetics, safety, and efficacy in comparison to intravenous administration (67). Combination of enzymes that break down the extracellular matrix have been investigated for the co-delivery of such therapeutics. This increases the available injection volume and the rate at which the therapeutic can reach the vasculature and increasing bioavailability (68). Hyaluronidase has been investigated for the localised delivery of rituximab and trastuzumab with both showing similar efficacy to intravenous injection (69). Additionally, a hyaluronic acid tyramine hydrogel has been combined with hyaluronidase and trastuzumab for controlled localised release of trastuzumab. The hydrogel was found to have a sustained release of trastuzumab over four weeks and additionally inhibited the growth of BT-474 cells *in vitro*. When investigated *in vivo* the hyaluronic acid tyramine gel loaded with hyaluronidase and trastuzumab inhibited tumour growth significantly compared to localised injection of trastuzumab alone. The gels also did not exhibit fibrous capsule formation after two weeks and improved the pharmacokinetic release profile in the plasma of mice. This should reduce off target side effects including cardiotoxicity although this was not investigated in the study (70). A thermosensitive PLGA-PEG-PLGA hydrogel loaded with trastuzumab and collagenase has also been investigated

for cancer treatment. This study showed the gel was retained in the tumour for at least 20 days and was found to increase apoptosis, reduce collagen density, and reduced toxicity compared to controls in BT474 tumour-bearing mice (71). Hyaluronic acid based microgels have also been used for the controlled release of trastuzumab to tumours. These microgels were formed using a combined microfluidic and photoclick chemistry method, these gels are also fluorescent to allow tracing of microparticles during testing. The microgels were found to be localised to the tumour with minimal levels detected systemically. Trastuzumab loaded microgels were found to significantly reduce tumour volume and apoptosis in comparison to trastuzumab delivered intravenously and subcutaneously (72). Single chain variable fragments (ScFv) are becoming more extensively researched and give the benefits of antibody therapy by using the antigen recognition site and removing the majority of the heavy chain antibody fragments. This allows a smaller molecule that can as effectively attach to the required antigen. Bifidobacterium has been shown to safely and effectively grow in hypoxic sites such as tumors after localized injection. These bacteria have been engineered to produce and secrete trastuzumab ScFv which was shown to reduce *in vitro* HER-2 positive cell growth. Additionally, the bacteria were locally injected into xenografted human HER2-positive tumours and found to inhibit tumour growth representing a promising strategy for localised sustained release of such therapeutics (73). Another promising strategy is the localised delivery of an alpha particle emitting radionucleotide ^{25}Ac-T linked to trastuzumab to target HER2 positive tumours via intraductal injection. It was found to deliver highly cytotoxic and targeted doses of radiation to tumours in a ductal carcinoma *in situ* model in mice. Localised delivery significantly reduced tumour growth compared to the same dose delivered intravenously (74). This offers a promising strategy for localised radiation therapy. HER-2 has also been targeted by thermosensitive liposomes by coating these particles in trastuzumab it allows specific targeting of HER-2 positive cells which only release their contents upon hyperthermic stimulation. Additionally, the authors also report a two components system that is composed of two HER-2 targeting liposomes that only differ in the substance they encapsulate. Once HER-2 receptor binding occurs by the liposomes they are engulfed by endocytosis, as these endosomes are up taken they go through the endocytosis pathway and they eventually fuse. Upon hyperthermic stimulation the endosomes release their contents into the endosomes in

healthy cells the cytotoxic drug can be contained within the endosome. However, when the two component system is used one component ruptures the endosome and the other releases its cytotoxic contents. This has limited effects on off target tissues as HER-2 is heavily over expressed in tumour cells and the particles alone in the healthy cells may not be sufficient to have a cytotoxic effect. Combining this with localised hyperthermic simulation makes this a highly specific and targeted system (75).

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Localised delivery of VEGF inhibitors such as bevacizumab have been extensively studied. Localised delivery of such factors will localise angiogenesis inhibition which would allow for reduced amount of drug to be used while additionally preventing off target side effects. A paper studying the effects of localised delivery of an oncolytic herpes virus hrR3 in addition to bevacizumab found that this is a promising treatment in an *in vivo* model of gastric cancer. Oncolytic herpes virus was administered to the tumour by intra tumoral injection and bevacizumb was administered internally. Although this is not a localised delivery of bevacizumab it was found to enhance localised therapy of oncolytic virus. Combination therapy of bevacizumab and hrR3 significantly reduced tumour growth compared to either treatment alone. Combination therapy also significantly reduced tumour angiogenesis compared to hrR3 alone and increased viral distribution as measure by lac Z (76). TACE is often used to block major vessels feeding a tumour but this then also leads to an angiogenesis response due to VEGF secretion. A study investigating the use of clinically available embolyitic beads added bevacizumab by layer by layer coating using alginate and poly-l-lysine for use as a localised and sustained controlled release system. A bevacizumab embolytic bead was successful developed and tested in 2D and 3D cell-based assays. The bevacizumab coated bead showed reduced cell sprouting of human umbilical vein endothelial cells comparable to the levels of bevacizumab alone. Although this study is promising for the use of these beads to enhance TACE therapy in highly vascularised tumours further studies are needed in order to test for its *in vivo* efficacy (77). Delivery to the brain can be often limited by the blood brain barrier, which can be challenging for localised therapy to brain cancers such as glioblastoma multiforme. It has been hypothesised that localised delivery of bevacizumab to glioblastoma could enhance its therapeutic benefit, but

due to the location of the brain this can be challenging. A group has used adeno associated viruses containing gene sequences for bevacizumab production in order for local neurons to produce bevacizumab and therefore bypassing problems associated with the blood brain barrier. The authors showed expression of bevacizumab mRNA in the brain and additionally showed increased survival, reduced tumour volume, and reduced blood vessels present in the tumour (78). Another study investigating the use of an adeno viral vector into the pleura of the lung in immunocompetent mice with metastatic lung cancer using a model of prostate cancer. Delivery of this adenovirus associated vector resulted in the sustained release of anti-human VEGF-A in lung epithelial fluid in the lung for the study duration of 40 weeks. In the treated mice there was increased survival, reduced tumour growth and reduced amount of blood vessels present in the lung (79). This further provides evidence that adenovirus vectors could be used for localised delivery and could serve as a viable option for localised delivery of VEGF inhibitors. A Poly (ethylene glycol)-poly (ε-caprolactone)-poly (ethylene glycol) (PEG-PCL-PEG, PECE) hydrogel has been used to deliver bevacizumab as an ophthalmic delivery system for glaucoma filtering surgery in rabbits and was found to reduce neovascularisation and scaring. Such hydrogel delivery systems could be considered for intratumorally delivery as a sustained release system in tumours while reducing off target side effects (80). Nanoparticles may also serve useful for the localised delivery of VEGF inhibitors. Mesoporous silica nanoparticles have been used for the localised delivery of VEGF to the eye. It has been shown that mesoporous silica nanoparticles loaded with bevacizumab reduced VEGF-induced endothelial cell proliferation, migration, and tube formation *in vitro* (81). Additionally, investigation of chitosan grafted-poly(ethylene glycol) methacrylate nanoparticles have been investigated for the controlled release of bevacizumab. This nanoparticles showed a prolonged release of bevacizumab and were also shown to be haemcompatible although further studies would be needed in order to assess the efficacy of such systems *in vivo* (82). Bevacizumab has also been loaded in poly (lactide-co-glycolide) (PLGA) nano particles and controlled release has been investigated in endothelial cells and were found reduce corneal neovascularization and retinal neovascularization. Additionally, SiO_2@LDH nano particles have been used, the surface was coated with bevacizumab for targeted therapy and loaded with doxorubicin or loaded with

doxorubicin only. The formulation was found to have anti angiogenic effects and additionally was cytotoxic due to the doxorubicin loading. In animals the SiO_2@LDH-bevacizumab-doxorubicin system was found to be the most effective formulation and significantly improved survival and reduced tumour volume (83). Additionally, this was one of the few studies to investigate the off-target effects of such therapies and was additionally found to prevent cardiotoxic effects and hepatic injury. Such systems have the potential to also be applied to anti-cancer therapies and could be beneficial in the field in tumour targeting and reducing off site cardiotoxicity.

Immune Checkpoint Inhibitor (ICI) Therapy

As stated previously, patients may have to discontinue ICI therapy due to various imAEs including cardiac complications, having an adverse effect on patient outcomes. It is essential that new preventative and therapeutic approaches are developed to help patients with ICI induced cardiotoxicity. Current strategies for local delivery of drugs in the cancer induced cardiotoxicity space focus on the delivery of chemotherapeutics directly to the tumour site in order to reduce the off-target cardiotoxicity. Local delivery of ICIs to cancer cells has been extensively researched and has shown promising and efficacious results (84–87). Numerous multimodal drug delivery vehicles have been employed including the use of hydrogels, microneedles, cells, and nanovesicles to deliver ICIs which has been excellently reviewed elsewhere (88). Alginate hydrogels have been used for the local delivery of two FDA approved ICI therapies celecoxib (cyclooxygenase 2 (COX-2) inhibitor) and programmed cell death protein 1 (PD-1) inhibitors in B16-F10 melanoma and 4T1 metastatic breast cancer in mice. The authors have shown that local delivery of these therapies improved T-cell mediated immunity, reduced immunosuppression, and angiogenesis (85). A biodegradable microneedle patch has been explored to deliver PD-1 inhibitors via pH responsive dextran nanoparticles to improve cost and efficacy in a B16-F10 mouse melanoma model. A single administration of a PD-1 inhibitor using this patch inhibited tumour growth in comparison with an intratumoral injection of PD-1 (86). Wang *et al* have shown that the conjugation of monoclonal antibodies against programmed death ligand (PD-L1) to platelets can result in a controlled release of anti-PD-L1 on activated platelets through platelet derived nanoparticles. This resulted in reduced recurrence of tumours after surgery and additionally reduced metastases in B16-F10 and

4TI mice through targeting of the surgical bed and targeting of circulating tumour cells (87). Cell derived nanovesicles are an emerging technology that has the potential to change drug and cell delivery. Xudong *et al* have reported the use of cell derived nanovesicles that display PD-1 which bind to PD-L1 on tumour cells to block inhibitory signals therefore enhancing T-cell immunity. These vesicles suppressed melanoma growth *in vivo* using B16-F10 mice (84). Thus, local delivery of ICIs using local and controlled release systems are a desirable way to minimise their systemic side effects while also improving upon the therapeutic index. However, these studies have failed to monitor the systemic toxicities which may be a major hurdle in the translation of this technology (84–87). Furthermore, these approaches are still in their infancy and will require extensive research before being approved for use.

Localised Delivery of Other Drugs

Several other products have been approved for commercial use for the localised delivery of chemotherapeutics to tumours. Abraxane® is a clinically approved formulation of paclitaxel bound to albumin approved for use in metastatic breast cancer, non-small cell lung cancer, pancreatic cancer, and ovarian cancer. Use of Abraxane® has shown improved complete remission rates in comparrision to solvent based paclitaxel in metastatic breast cancer (89). Marqibo® is a clinically approved liposomal form of vincristine approved for the treatment of Philadelphia chromosome negative acute lymphoblastic leukaemia representing an advancement in drug delivery to improve efficacy and reduce off target toxicities (90). Giladel® is a carmustine loaded polyanhydride wafer implant, in this system carmustine is loaded in a 1,3-bis(p-carboxyphenoxy) propane and sebacic acid copolymer matrix. The polymer matrix slowly degrades and releases drug into the site and is used for the treatment of recurrent brain cancer (91–93). Zoladex® is a PLGA based implantable cylinder that is used for treatment of prostate and breast cancers and allows the release of drugs for up to three months (93,94). Eligard® is an injectable implant that forms in situ for the release of leuprolide acetate that is used in cancers such as breast cancer and prostate cancer that are hormone responsive. It is composed of a drug and a matrix composed of PLGA in N-methyl pyrrolidone which when combined result in the formation of a solid implant upon injection (93). Viadur® is used for palliative treatment in

patients with advanced prostate cancer, it is a miniature implant that is composed of a titanium alloy reservoir, polyurethane membrane, elastomeric piston and a diffusion moderator. This implant in non-biodegradable and allows for the sustained drug release for up to one year (93,95). A thermosensitive, biodegradable PLGA and PEG hydrogel named OncoGel® has been developed for treatment in brain tumours post resection. This gel is liquid at room temperature and undergoes a liquid to gel transition in the body solidifying upon injection, This gel is loaded with paclitaxel and can be combined with other treatments for use in brain tumour applications (93,96,97).

The use of endobronchial intratumoral chemotherapy (EITC) has been used in order to deliver several drugs to tumours. EITC combines the use of a flexible bronchoscope to access the lungs which is then attached to a needle-catheter which allows for the localised injection of chemotherapy into the tumour site (93). The use of 5-flurouracil was used with EITC in a trial of 65 patients, 56 patients responded positively to the treatment and increased the area of luminal opening from a mean of 22% to 58.5% (98). EITC has also been used for the localised delivery of cisplatin and it was found that this therapy could be beneficial in reducing airway obstruction and prevention of post obstruction pneumonias in patients with inoperable lung cancers (99,100). Such approaches could be used with injectable hydrogels or nanoparticles which would allow a more sustained release of drug due to the prolonged life of hydrogels within the tumour (93).

Polyurethanes have been used in order as synthetic polymers capable of delivering drugs to tumours. Polyurethanes are often selected due to their biocompatibility, mechanical properties, and their ability to degrade into non-cytotoxic products (93,101). A thermosresponsive polyurethane membrane was developed which allowed on off switching to allow controlled on demand release of paclitaxel. This membrane could switch on by heating to 44 degrees and release drug in a time dependent manner, upon cooling of the membrane to 37-degrees drug release stopped. Such membranes have the potential to be implanted in the body and allow the on demand release of drug although further research is needed in order to translate this technology to patient use (102). Polyurethanes have also been developed for the local treatment of gastric tumours around gastrointestinal stents using paclitaxel. In this study

the authors tested there stent *in vivo* and observed a 65.5% reduction in tumour growth in comparison to untreated controls (103). Another group used polyurethane films in order to treat pancreatic cancer by loading a film with gemcitabine this device had the advantage of being easily placed in the body, being refillable, and easily removed from the body. Low dosages of gemcitabine was able to slow tumour growth and prevent tumour regrowth after surgery in mice (92).

Table 1 Approved therapeutic products for targeted delivery

Therapeutic	**Drug**	**Delivery Vehicle**	**Indication**	**Outcomes**
Doxil®	Doxorubicin	Pegylated liposome	Approved for AIDS related Kaposi's sarcoma, breast cancer, ovarian cancer, and other tumours	Improved half-life and tumour drug accumulation while mitigating cardiotoxicity (52,53)
Myocet®	Doxorubicin	Non-pegylated liposome	Approved for use in combination with cyclophosphamide in metastatic breast cancer	Similar response rates to doxorubicin but reduced rates of cardiotoxicity (56,57)
DanuoXome®	Daunorubicin	Non-pegylated liposome	Approved for use in AIDS related Kaposi's sarcoma	Improved drug half-life but prevention of cardiotoxicity in comparrision to free daunorubicin is unclear (61)
Marqibo®	Vincristine	Non-pegylated liposome	Approved for Philadelphia chromosome negative acute lymphoblastic leukaemia during relapse	Comparative data to free vincristine not available. Marqibo® trial reported cardiac arrest in 3% of patients (50)
Abraxane®	Paclitaxel	Albumin conjugation	Approved for metastatic breast cancer, non-small	Approval in complete remission rates

			cell lung cancer, pancreatic cancer, and ovarian cancer	compared to free paclitaxel. Similar rates of cardiotoxicity (89)

Table 2: Localized strategies for tumour targeting in preclinical studies.

Approach	Drug	Delivery Vehicle	Results
Hyper branched polymer	Doxorubicin	Polyethylene glycol	Tumour specific targeting and significant reductions in tumour size (64)
Drug polymer conjugation	Doxorubicin and aminoglutethimide	Poly glycosylic acid	Reduced tumour size and reduce lung metastases by 90% in a preclinical metastatic triple-negative breast cancer murine model (64)
Metronomic nano delivery	Doxorubicin	H-ferritin nanoparticle	Improved anti-tumour effect, reduced chemoresistance, and mitigation of cardiotoxicity in comparrision to doxorubicin (104)
Exosomes	Doxorubicin	Exosomes	Anti-tumour effects comparable to doxorubicin. Exosomes reduce cardiac doxorubicin concentration by 40% (105)
Hydrogel delivery with hyaluronidase	Trastuzumab	Hyaluronic acid tyramine	Sustained release over four weeks. Significantly reduced tumour size *in vivo* in comparrision to localized injection of trastuzumab (70)
Hydrogel delivery with collagenase	Trastuzumab	PLGA-PEG-PLGA	Tumour retention for up to 20 days. Enhanced apoptotic cell death and reduced toxicity compared to controls (71)
Microgels	Trastuzumab	Hyaluronic acid	Superior tumour localization and reduced off target accumulation. Increased reduction in tumour volume in comparrision to intravenous and subcutaneous injection (72)
Localized bacterial delivery to produce single chain	Trastuzumab single chain variable fragments	Bifidobacterium	Sustained release and inhibition of tumour growth (73)

variable fragments			
Localized radiotherapy and trastuzumab	Alpha particle emitting radionucleotide ^{25}Ac-T linked to trastuzumab	Intraductal injection	Reduced tumour growth *in vivo* in comparrision to intravenous injection (74)
Oncolytic herpes virus hrR3	Oncolytic virus and bevacizumab	Intratumoral injection	Combinational approach reduced tumour size and angiogenesis compared to either treatment alone (76)
TACE	Bevacizumab	TACE beads	Reduced endothelial cell sprouting *in vitro* (77)
Adeno associated viruses for delivery of bevacizumab gene sequences	Bevacizumab	Adenovirus	Increased survival, reduced tumour volume, decreased angiogenesis for glioblastoma multiforme (78)
Adenoviral vector for anti-VEGF delivery	Anti-VEGF A antibody	Adenovirus	Sustained release for up to 40 weeks in mice increased survival, reduced tumour growth, reduced angiogenesis (79)
Nanoparticle delivery	Bevacizumab and doxorubicin	SiO_2@LDH	Improved survival and reduced tumour volume (83)
Hydrogel delivery for ICI therapy	Celecoxib and PD-1 antibodies	Alginate hydrogel	Improved T-cell immunity, reduced immunosuppression, and angiogenesis (85)
Microneedle patch with drug loaded nanoparticles	PD-1 inhibitor	Microneedle patch and pH responsive dextran nanoparticles	Microneedle patch inhibited tumour growth in comparrision to intratumoral injection (86)
Platelet delivery of anti-PD-L1	PD-L1 inhibitor	Platelet derived nanoparticles	Reduced reoccurrence and metastases (87)

Exogenously Triggered Systems

In order to efficaciously combat cancer-therapy induced cytotoxicity, exogenously triggered drug delivery systems, which capitalise on external stimuli such as temperature, ultrasound, and magnetic fields can be employed.

Thermoresponsive drug delivery systems

Thermoresponsive drug delivery systems draw primarily upon the marked response of nanocarrier particles to non-linear, sharp variations in temperatures within a certain setting. An ideal thermoresponsive system ought to respond to subtle, yet non-linear, changes within a tissue milieu, thereby triggering the release of the loaded drug dose (106). In practice, this notion can be extrapolated to suggest that such systems should retain their drug loads at the standard human body temperatures and release their drug load to tumours that are locally heated to 40-42 degrees Celsius (107). Pertinently, thermoresponsive liposomes (TSLs) are touted to be the most technologically advanced thermoresponsive nanosystems (108). Doxorubicin-loaded TSLs have demonstrated unparalleled safety and efficacy in several clinical trials. For instance, doxorubicin-loaded TSLs have progressed to phase II clinical trials for the treatment of breast cancer (109). In the same vain, doxorubicin-loaded TSLs have recently entered phase III clinical trials for the chemotherapeutic treatment of hepatocellular carcinoma (110). Nevertheless, the overarching challenges that ensue in the curation of thermoresponsive nanocarriers stem from the fact that the curated particles must both be safe and sensitive enough to respond to subtle variations in temperature. To this end, thermoresponsive liposomal drug delivery systems are deemed the most clinically advanced and boast the greatest therapeutic potential.

Magnetic nanoparticle based systems

The salient feature of magnetically triggered nanoparticle based systems is the variable responsiveness of the particles to alterations in magnetic field, increments in temperature, or both (111). The employment of magnetically responsive systems also lends to the possibility of conducting magnetic resonance imaging (MRI) of the tumour site simultaneously (6). The concurrent application of diagnostics and therapy within a single system ameliorates the efficiency of the system, thereby championing the so called “theranostic” approach (112). In order to conduct this approach, a magnetically responsive nanocarrier is first injected in the target site. In doing so, the extracorporeal magnetic field is directed towards the target tumour site through the means of magnetic guidance. Interestingly, such drug delivery systems have boasted remarkable rates of drug accumulation within solid tumours in models. The

most viable candidates for this approach are core-shell nanoparticles and magnetoliposomes (113). While most core-shell models have demonstrated encouraging results in *in vitro* studies, only a handful have boasted noteworthy anticancer potential during *in vivo* studies (114,115). Perhaps the most detrimental roadblock to the uptake of such models is the limitation that occurs secondary to mechanical drug entrapment. In order to evade this issue, the nanoparticle in question can be covalently linked to the desired therapeutic drug (116). Another downside of adopting this approach is that magnetically stimulated delivery systems are limited to solid tumours and nodules, and often manifest no efficacy in the treatment of cancer metastasis or dissemination (116).

Ultrasound triggered drug delivery systems

The employment of ultrasound stimulated drug delivery systems lends to the possibility of spatiotemporal control of drug release within the diseased tissue, thereby circumventing harmful drug-related adverse effects on the healthy tissues (117). In addition to affording narrow spatiotemporal control, ultrasound triggered drug delivery systems remain non-invasive and do not necessitate harmful exposure to ionising radiation (118). Furthermore, the frequency of the ultrasound can be manipulated to vary the depth of the tissue invasion required. Nevertheless, it is equally important to bear the ramifications of ultrasound triggered drug delivery systems in mind. Ultrasound triggered systems, for instance, can amplify the vessel permeability, leading to a paradoxical increase in the risk of cancer dissemination (119). Due to the ability of ultrasound-mediated drug delivery systems to create a pore in the cell membrane, the drug can be delivered directly into cytosol, thereby evading degradative endocytosis (120).

Delivery of Cardioprotectants to the Heart

Another possible option of preventing ICI induced cardiotoxicity is the localised delivery of cardioprotectants to the heart. It can be considered for the patients with haematological malignancies where localised ICI delivery is not an option. Biomaterial-enhanced local delivery systems have been extensively researched in the cardiac field and include the delivery of cells, drugs, and growth factors incorporating minimally invasive strategies (121). Minimally invasive delivery strategies that can be used to target therapies to the heart which can be incorporated with

minimally invasive procedures include epicardial, intracoronary, endocardial, and transvascular approaches this could improve the translatability of such approaches outlined in Figure 3. Studies have shown that the delivery of embryonic and adipose derived mesenchymal stem cells can improve cardiac function in mouse models of chemotherapy induced cardiotoxicity (45,46,122). Data of the first and only study using stem cells to treat chemotherapy induced cardiotoxicity was recently published. The phase I trial randomised 31 subjects to receive either 1 x 10^8 allogeneic bone marrow derived mesenchymal stromal cells or delivery vehicle. The study showed safety and feasible and provides information for the conduction of larger trials. Secondary outcomes showed a trend towards significance in the 6 minute walk test and a significant improvement in the Minnesota Living with Heart Failure Questionnaire (123). Biomaterial carriers could be used to enhance cell and drug delivery strategies by allowing local delivery of therapy to the heart (121). For example, systemic use of dexrazoxane, the only FDA approved cardioprotectant against anthracycline induced cardiotoxicity was under scrutiny especially in paediatric populations by the regulatory bodies amid concerns of its association with secondary malignancy (124,125). Local delivery of dexrazoxane to the heart has the potential to alleviate such concerns surrounding the use of dexrazoxane.

Fig. 3 Minimally invasive delivery strategies that could be used for localised delivery of therapeutics to the heart

Medical device technology incorporating minimally invasive strategies could have great potential in the chemotherapy induced cardiotoxicity and ICI induced myocarditis space. Garcia *et al* have developed a minimally invasive device that allows the delivery of biomaterials to the heart using the pericardial space as a novel site of delivery of biomaterials. This device has had success in delivering a drug loaded polyethylene glycol (PEG) hydrogel in both rodent and porcine models. The amiodarone loaded PEG hydrogel showed a success in a porcine model of atrial fibrillation by reducing the duration of atrial fibrillation compared with delivery of gel alone. Furthermore, off target amiodarone levels were significantly reduced in comparison with systemic delivery after 28 days (126,127). A recent study by Whyte *et al* has shown promising results for a refillable cardiac reservoir that can

be placed on the epicardium in a minimally invasive fashion using a mini-thoracotomy for the delivery of stem cells to the heart post myocardial infarction. This device can easily be refilled through a subcutaneous port and allows multiple dosages of cells or drugs to the heart in a minimally invasive fashion. Refills of cells into this device have shown to significantly increase LVEF compared to no treatment and to cell injection alone (128). Such devices have the potential to allow local cell and drug therapies that could combat issues associated with ICI induced myocarditis.

Other potential treatments that have been shown to decrease the rates of cardiotoxicity in preclinical models could also be considered for localised cardioprotectant delivery to the heart. Resveratrol which is a promising polyphenol compound has been investigated in several preclinical studies. As well as providing cardioprotective effects resveratrol has also shown anti-tumour efficacy (129–135). However, resveratrol often has poor oral bioavailability, combining resveratrol with nanoparticles could improve its bioavailability in the body and could enhance its cardioprotective effects (136). It is a potent antioxidant which can prevent the formation of reactive oxygen species produced by anthracyclines such as doxorubicin and is also thought to be protective through activation of the sirtunin pathways (107,108). Curcumin, which is a component of turmeric, has also shown promising effects in preventing chemotherapy induced cardiotoxicity and has anti-cancer effects. Both resveratrol and curcumin have bin co-administer using nanoparticles and it has been found that co-delivery mitigates doxorubicin induced cardiotoxicity in a preclinical model (139).

Conclusion

Chemotherapeutics including newly introduced ICI therapy give patients greater options for treatment but is drawn back due to its systemic toxicity including myocarditis. Chemotherapy induced cardiotoxicity is a potentially fatal complication. Holding the therapy or using systemic steroids to curb the complications may reduce the effectiveness of the therapy. Hence, there is an unmet need to develop new delivery strategies to either deliver the chemotherapeutic locally to the tumour site to reduce the off-target complications or to deliver cardioprotectants directly to the heart for the prevention of chemotherapy induced myocarditis.

Authors' contributions

Aamir Hameed and Garry P. Duffy had the idea for the article. Aamir Hameed, David S. Monahan and Talal Almas performed the literature search and data analysis. David S. Monahan, Talal Almas and Aamir Hameed drafted the manuscript. Robert Wyile created the illustrations. Aamir Hameed, Garry P. Duffy, Faisal H. Cheema, David S. Monahan and Talal Almas critically revised the work.

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Compliance with ethical standards

Competing interests

The authors declare no conflicts of interests and have no relation to industry.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018;68(6):394–424. Available from: https://onlinelibrary.wiley.com/doi/abs/10.3322/caac.21492

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin [Internet]. 2018 Jan 1;68(1):7–30. Available from: https://doi.org/10.3322/caac.21442

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020 Jan;70(1):7–30.

4. Herrmann J. Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia. Nat Rev Cardiol [Internet]. 2020; Available from: https://doi.org/10.1038/s41569-020-0348-1

5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ES. Eur Heart J [Internet]. 2016 Aug 24;37(36):2768–801. Available from: https://doi.org/10.1093/eurheartj/ehw211

6. Ma J, Wang Y, Zheng D, Wei M, Xu H, Peng T. Rac1 signalling mediates doxorubicin-induced cardiotoxicity through both reactive oxygen species-dependent and -independent pathways. Cardiovasc Res [Internet]. 2012 Oct 1;97(1):77–87. Available from: https://doi.org/10.1093/cvr/cvs309

7. Han X, Zhou Y, Liu W. Precision cardio-oncology: understanding the cardiotoxicity of cancer therapy. NPJ Precis Oncol [Internet]. 2017 Sep 12;1(1):31. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29872712

8. Khawaja MZ, Cafferkey C, Rajani R, Redwood S, Cunningham D. Cardiac complications and manifestations of chemotherapy for cancer. Heart [Internet]. 2014 Jul 15;100(14):1133 LP – 1140. Available from: http://heart.bmj.com/content/100/14/1133.abstract

9. Lipshultz SE, Karnik R, Sambatakos P, Franco VI, Ross SW, Miller TL. Anthracycline-related cardiotoxicity in childhood cancer survivors. Curr Opin Cardiol [Internet]. 2014;29(1). Available from:

https://journals.lww.com/co-cardiology/Fulltext/2014/01000/Anthracycline_related_cardiotoxicity_in_childhood.15.aspx

10. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis. Eur J Cancer [Internet]. 2013 Sep 1;49(13):2900–9. Available from: https://doi.org/10.1016/j.ejca.2013.04.030

11. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. N Engl J Med [Internet]. 2006;355(15):1572–82. Available from: https://doi.org/10.1056/NEJMsa060185

12. Vejpongsa P, Yeh ETH. Prevention of Anthracycline-Induced Cardiotoxicity: Challenges and Opportunities. J Am Coll Cardiol [Internet]. 2014;64(9):938–45. Available from: http://www.sciencedirect.com/science/article/pii/S0735109714043162

13. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? Prog Cardiovasc Dis [Internet]. 2010;53(2):105–13. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20728697

14. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. Cancer [Internet]. 2003;97(11):2869–79. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.11407

15. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane database Syst Rev [Internet]. 2012 Apr 18;2012(4):CD006243–CD006243. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22513938

16. Shah MA. Update on Metastatic Gastric and Esophageal Cancers. J Clin Oncol [Internet]. 2015 Apr 27;33(16):1760–9. Available from: https://doi.org/10.1200/JCO.2014.60.1799

17. Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, et al. Trastuzumab-Associated Cardiac Adverse Effects in the Herceptin Adjuvant Trial. J Clin Oncol [Internet]. 2007 Sep 1;25(25):3859–65. Available from: https://doi.org/10.1200/JCO.2006.09.1611

18. Advani PP, Ballman K V, Dockter TJ, Colon-Otero G, Perez EA. Long-Term Cardiac Safety Analysis of NCCTG N9831 (Alliance) Adjuvant Trastuzumab Trial. J Clin Oncol [Internet]. 2015 Sep 21;34(6):581–7. Available from: https://doi.org/10.1200/JCO.2015.61.8413

19. de Azambuja E, Procter MJ, van Veldhuisen DJ, Agbor-Tarh D, Metzger-Filho O, Steinseifer J, et al. Trastuzumab-Associated Cardiac Events at 8 Years of Median Follow-Up in the Herceptin Adjuvant Trial (BIG 1-01). J Clin Oncol [Internet]. 2014 Jun 9;32(20):2159–65. Available from: https://doi.org/10.1200/JCO.2013.53.9288

20. Romond EH, Jeong J-H, Rastogi P, Swain SM, Geyer CE, Ewer MS, et al. Seven-Year Follow-Up Assessment of Cardiac Function in NSABP B-31, a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel (ACP) With ACP Plus Trastuzumab As Adjuvant Therapy for Patients With Node-Positive, Human Epidermal Gr. J Clin Oncol [Internet]. 2012 Sep 17;30(31):3792–9. Available from: https://doi.org/10.1200/JCO.2011.40.0010

21. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, et al. 2 years versus 1

year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet [Internet]. 2013;382(9897):1021–8. Available from: http://www.sciencedirect.com/science/article/pii/S0140673613610946

22. Ewer MS, Lippman SM. Type II Chemotherapy-Related Cardiac Dysfunction: Time to Recognize a New Entity. J Clin Oncol [Internet]. 2005 May 1;23(13):2900–2. Available from: https://doi.org/10.1200/JCO.2005.05.827

23. Cote GM, Sawyer DB, Chabner BA. ERBB2 Inhibition and Heart Failure. N Engl J Med [Internet]. 2012 Nov 28;367(22):2150–3. Available from: https://doi.org/10.1056/NEJMcibr1203156

24. Lenihan D, Suter T, Brammer M, Neate C, Ross G, Baselga J. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. Ann Oncol Off J Eur Soc Med Oncol [Internet]. 2011/06/10. 2012 Mar;23(3):791–800. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21665955

25. Krop IE, Suter TM, Dang CT, Dirix L, Romieu G, Zamagni C, et al. Feasibility and Cardiac Safety of Trastuzumab Emtansine After Anthracycline-Based Chemotherapy As (neo)Adjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early-Stage Breast Cancer. J Clin Oncol [Internet]. 2015 Feb 23;33(10):1136–42. Available from: https://doi.org/10.1200/JCO.2014.58.7782

26. Piccart-Gebhart M, Holmes E, Baselga J, de Azambuja E, Dueck AC, Viale G, et al. Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. J Clin Oncol [Internet]. 2015 Nov 23;34(10):1034–42. Available from: https://doi.org/10.1200/JCO.2015.62.1797

27. Ghatalia P, Morgan CJ, Je Y, Nguyen PL, Trinh Q-D, Choueiri TK, et al. Congestive heart failure with vascular endothelial growth factor receptor tyrosine kinase inhibitors. Crit Rev Oncol Hematol [Internet]. 2015;94(2):228–37. Available from: http://www.sciencedirect.com/science/article/pii/S1040842814002169

28. Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol [Internet]. 2013;14(10):933–42. Available from: http://www.sciencedirect.com/science/article/pii/S1470204513703358

29. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. N Engl J Med [Internet]. 2013 Aug 21;369(8):722–31. Available from: https://doi.org/10.1056/NEJMoa1303989

30. Qi W-X, Shen Z, Tang L-N, Yao Y. Congestive heart failure risk in cancer patients treated with vascular endothelial growth factor tyrosine kinase inhibitors: a systematic review and meta-analysis of 36 clinical trials. Br J Clin Pharmacol [Internet]. 2014 Oct;78(4):748–62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24661224

31. Steingart RM, Bakris GL, Chen HX, Chen M-H, Force T, Ivy SP, et al. Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors. Am Heart J [Internet]. 2012;163(2):156–63. Available from: http://www.sciencedirect.com/science/article/pii/S0002870311007782

32. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol [Internet]. 2013;14(6):552–62. Available from:

http://www.sciencedirect.com/science/article/pii/S1470204513700937

33. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol [Internet]. 2018 May 8;2:13. Available from: https://pubmed.ncbi.nlm.nih.gov/30202791

34. Ewer MS, Suter TM, Lenihan DJ, Niculescu L, Breazna A, Demetri GD, et al. Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: A comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events. Eur J Cancer [Internet]. 2014;50(12):2162–70. Available from: http://www.sciencedirect.com/science/article/pii/S0959804914006819

35. Moslehi JJ, Salem J-E, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet (London, England) [Internet]. 2018 Mar 10;391(10124):933. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29536852

36. Leach DR, Krummel MF, Allison JP. Enhancement of Antitumor Immunity by CTLA-4 Blockade. Science (80-) [Internet]. 1996 Mar 22;271(5256):1734 LP – 1736. Available from: http://science.sciencemag.org/content/271/5256/1734.abstract

37. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med [Internet]. 2015/05/31. 2015 Jul 2;373(1):23–34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26027431

38. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med [Internet]. 2015/04/20. 2015 May 21;372(21):2006–17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25891304

39. Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol [Internet]. 2018/11/12. 2018 Dec;19(12):1579–89. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30442497

40. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med [Internet]. 2016 Nov 2;375(18):1749–55. Available from: https://doi.org/10.1056/NEJMoa1609214

41. Mahmood SS, Fradley MG, Cohen J V, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol [Internet]. 2018/03/19. 2018 Apr 24;71(16):1755–64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29567210

42. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med [Internet]. 2018 Jan 10;378(2):158–68. Available from: https://doi.org/10.1056/NEJMra1703481

43. Lucchesi M, Sardi I, Puppo G, Chella A, Favre C. The dawn of "immune-revolution" in children: early experiences with checkpoint inhibitors in childhood malignancies. Cancer Chemother Pharmacol [Internet]. 2017 Dec;80(6):1047—1053. Available from: https://doi.org/10.1007/s00280-017-3450-2

44. Merchant MS, Wright M, Baird K, Wexler LH, Rodriguez-Galindo C, Bernstein D, et al. Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors. Clin Cancer Res [Internet].

2015/11/03. 2016 Mar 15;22(6):1364–70. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26534966

45. Pınarlı FA, Turan NN, Güçlü Pınarlı F, Okur A, Sönmez D, Ulus T, et al. Resveratrol and Adipose-derived Mesenchymal Stem Cells Are Effective in the Prevention and Treatment of Doxorubicin Cardiotoxicity in Rats. Pediatr Hematol Oncol [Internet]. 2013 Mar 13;30(3):226–38. Available from: https://doi.org/10.3109/08880018.2012.762962

46. Singla DK, Ahmed A, Singla R, Yan B. Embryonic Stem Cells Improve Cardiac Function in Doxorubicin-Induced Cardiomyopathy Mediated through Multiple Mechanisms. Cell Transplant [Internet]. 2012;21(9):1919–30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3402598/

47. Räsänen M, Degerman J, Nissinen TA, Miinalainen I, Kerkelä R, Siltanen A, et al. VEGF-B gene therapy inhibits doxorubicin-induced cardiotoxicity by endothelial protection. Proc Natl Acad Sci U S A [Internet]. 2016/10/31. 2016 Nov 15;113(46):13144–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27799559

48. Pons-Faudoa FP, Ballerini A, Sakamoto J, Grattoni A. Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases. Biomed Microdevices [Internet]. 2019 May 18;21(2):47. Available from: https://pubmed.ncbi.nlm.nih.gov/31104136

49. Batist G. Cardiac safety of liposomal anthracyclines. Cardiovasc Toxicol [Internet]. 2007;7(2):72–4. Available from: https://doi.org/10.1007/s12012-007-0014-4

50. Xing M, Yan F, Yu S, Shen P. Efficacy and Cardiotoxicity of Liposomal Doxorubicin-Based Chemotherapy in Advanced Breast Cancer: A Meta-Analysis of Ten Randomized Controlled Trials. PLoS One [Internet]. 2015 Jul 23;10(7):e0133569–e0133569. Available from: https://pubmed.ncbi.nlm.nih.gov/26204517

51. Mohamed M, Abu Lila AS, Shimizu T, Alaaeldin E, Hussein A, Sarhan HA, et al. PEGylated liposomes: immunological responses. Sci Technol Adv Mater [Internet]. 2019 Jun 26;20(1):710–24. Available from: https://pubmed.ncbi.nlm.nih.gov/31275462

52. Gabizon A, Catane R, Uziely B, Kaufman B, Safra T, Cohen R, et al. Prolonged Circulation Time and Enhanced Accumulation in Malignant Exudates of Doxorubicin Encapsulated in Polyethylene-glycol Coated Liposomes. Cancer Res [Internet]. 1994;54(4):987–92. Available from: https://cancerres.aacrjournals.org/content/54/4/987

53. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal Formulations in Clinical Use: An Updated Review. Pharmaceutics [Internet]. 2017;9(2). Available from: https://www.mdpi.com/1999-4923/9/2/12

54. Kanter PM, Bullard GA, Pilkiewicz FG, Mayer LD, Cullis PR, Pavelic ZP. Preclinical toxicology study of liposome encapsulated doxorubicin (TLC D-99): comparison with doxorubicin and empty liposomes in mice and dogs. In Vivo [Internet]. 1993;7(1):85—95. Available from: http://europepmc.org/abstract/MED/8504212

55. Balazsovits JAE, Mayer LD, Bally MB, Cullis PR, McDonell M, Ginsberg RS, et al. Analysis of the effect of liposome encapsulation on the vesicant properties, acute and cardiac toxicities, and antitumor efficacy of doxorubicin. Cancer Chemother Pharmacol [Internet]. 1989;23(2):81–6. Available from: https://doi.org/10.1007/BF00273522

56. Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, et al. Reduced cardiotoxicity

and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol [Internet]. 2001 Mar 1;19(5):1444–54. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11230490

57. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. Cancer [Internet]. 2002 Jan 1;94(1):25–36. Available from: https://doi.org/10.1002/cncr.10201

58. Gill PS, Espina BM, Muggia F, Cabriales S, Tulpule A, Esplin JA, et al. Phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin. J Clin Oncol [Internet]. 1995 Apr;13(4):996–1003. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7707129

59. Fumagalli L, Zucchetti M, Parisi I, Viganò MG, Zecca B, Careddu A, et al. The pharmacokinetics of liposomal encapsulated daunorubicin are not modified by HAART in patients with HIV-associated Kaposi's sarcoma. Cancer Chemother Pharmacol [Internet]. 2000;45(6):495–501. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10854138

60. Tulpule A, Yung RC, Wernz J, Espina BM, Myers A, Scadden DT, et al. Phase II trial of liposomal daunorubicin in the treatment of AIDS-related pulmonary Kaposi's sarcoma. J Clin Oncol [Internet]. 1998 Oct 1;16(10):3369–74. Available from: https://doi.org/10.1200/JCO.1998.16.10.3369

61. Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol [Internet]. 1996 Aug 1;14(8):2353–64. Available from: https://doi.org/10.1200/JCO.1996.14.8.2353

62. Taha MS, Padmakumar S, Singh A, Amiji MM. Critical quality attributes in the development of therapeutic nanomedicines toward clinical translation. Drug Deliv Transl Res [Internet]. 2020;10(3):766–90. Available from: https://doi.org/10.1007/s13346-020-00744-1

63. Pearce AK, Simpson JD, Fletcher NL, Houston ZH, Fuchs A V, Russell PJ, et al. Localised delivery of doxorubicin to prostate cancer cells through a PSMA-targeted hyperbranched polymer theranostic. Biomaterials. 2017 Oct;141:330–9.

64. Arroyo-Crespo JJ, Armiñán A, Charbonnier D, Balzano-Nogueira L, Huertas-López F, Martí C, et al. Tumor microenvironment-targeted poly-L-glutamic acid-based combination conjugate for enhanced triple negative breast cancer treatment. Biomaterials [Internet]. 2018;186:8–21. Available from: http://www.sciencedirect.com/science/article/pii/S0142961218306604

65. Facciorusso A. Drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma: Current state of the art. World J Gastroenterol [Internet]. 2018 Jan 14;24(2):161–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29375202

66. Malagari K, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, et al. Prospective Randomized Comparison of Chemoembolization with Doxorubicin-Eluting Beads and Bland Embolization with BeadBlock for Hepatocellular Carcinoma. Cardiovasc Intervent Radiol [Internet]. 2010;33(3):541–51. Available from: https://doi.org/10.1007/s00270-009-9750-0

67. Jackisch C, Stroyakovskiy D, Pivot X, Ahn JS, Melichar B, Chen S-C, et al. Subcutaneous vs Intravenous Trastuzumab for Patients With ERBB2-Positive Early Breast Cancer: Final Analysis of the HannaH Phase 3 Randomized Clinical Trial. JAMA Oncol [Internet]. 2019/05/09. 2019 May 1;5(5):e190339–e190339. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30998824

68. Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv [Internet]. 2007 Jul 1;4(4):427–40. Available from: https://doi.org/10.1517/17425247.4.4.427

69. Shpilberg O, Jackisch C. Subcutaneous administration of rituximab (MabThera) and trastuzumab (Herceptin) using hyaluronidase. Br J Cancer [Internet]. 2013/09/03. 2013 Sep 17;109(6):1556–61. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24002601

70. Xu K, Lee F, Gao S, Tan M-H, Kurisawa M. Hyaluronidase-incorporated hyaluronic acid–tyramine hydrogels for the sustained release of trastuzumab. J Control Release [Internet]. 2015;216:47–55. Available from: http://www.sciencedirect.com/science/article/pii/S0168365915300614

71. Pan A, Wang Z, Chen B, Dai W, Zhang H, He B, et al. Localized co-delivery of collagenase and trastuzumab by thermosensitive hydrogels for enhanced antitumor efficacy in human breast xenograft. Drug Deliv [Internet]. 2018 Nov;25(1):1495–503. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29943651

72. Chen J, Huang K, Chen Q, Deng C, Zhang J, Zhong Z. Tailor-Making Fluorescent Hyaluronic Acid Microgels via Combining Microfluidics and Photoclick Chemistry for Sustained and Localized Delivery of Herceptin in Tumors. ACS Appl Mater Interfaces [Internet]. 2018 Jan 31;10(4):3929–37. Available from: https://doi.org/10.1021/acsami.7b15832

73. Kikuchi T, Shimizu H, Akiyama Y, Taniguchi S. In situ delivery and production system of trastuzumab scFv with Bifidobacterium. Biochem Biophys Res Commun [Internet]. 2017;493(1):306–12. Available from: http://www.sciencedirect.com/science/article/pii/S0006291X17317862

74. Yoshida T, Jin K, Song H, Park S, Huso DL, Zhang Z, et al. Effective treatment of ductal carcinoma in situ with a HER-2- targeted alpha-particle emitting radionuclide in a preclinical model of human breast cancer. Oncotarget [Internet]. 2016 May 31;7(22):33306–15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27119227

75. Kullberg M, Mann K, Owens JL. A two-component drug delivery system using Her-2-targeting thermosensitive liposomes. J Drug Target [Internet]. 2009 Jan 1;17(2):98–107. Available from: https://doi.org/10.1080/10611860802471562

76. Deguchi T, Shikano T, Kasuya H, Nawa A, Fujiwara S, Takeda S, et al. Combination of the tumor angiogenesis inhibitor bevacizumab and intratumoral oncolytic herpes virus injections as a treatment strategy for human gastric cancers. Hepatogastroenterology [Internet]. 2012 Sep;59(118):1844—1850. Available from: https://doi.org/10.5754/hge11566

77. Sakr OS, Berndt S, Carpentier G, Cuendet M, Jordan O, Borchard G. Arming embolic beads with anti-VEGF antibodies and controlling their release using LbL technology. J Control Release [Internet]. 2016;224:199–207. Available from: http://www.sciencedirect.com/science/article/pii/S0168365916300098

78. Hicks MJ, Funato K, Wang L, Aronowitz E, Dyke JP, Ballon DJ, et al. Genetic modification of neurons to

express bevacizumab for local anti-angiogenesis treatment of glioblastoma. Cancer Gene Ther [Internet]. 2014/12/12. 2015 Jan;22(1):1–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25501993

79. Watanabe M, Boyer JL, Crystal RG. AAVrh.10-mediated genetic delivery of bevacizumab to the pleura to provide local anti-VEGF to suppress growth of metastatic lung tumors. Gene Ther [Internet]. 2010/07/01. 2010 Aug;17(8):1042–51. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20596059

80. Peng R, Qin G, Li X, Lv H, Qian Z, Yu L. The PEG-PCL-PEG Hydrogel as an Implanted Ophthalmic Delivery System after Glaucoma Filtration Surgery; a Pilot Study. Med hypothesis, Discov Innov Ophthalmol J [Internet]. 2014;3(1):3–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24804274

81. Sun J-G, Jiang Q, Zhang X-P, Shan K, Liu B-H, Zhao C, et al. Mesoporous silica nanoparticles as a delivery system for improving antiangiogenic therapy. Int J Nanomedicine [Internet]. 2019 Feb 25;14:1489–501. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30880960

82. Savin C-L, Popa M, Delaite C, Costuleanu M, Costin D, Peptu CA. Chitosan grafted-poly(ethylene glycol) methacrylate nanoparticles as carrier for controlled release of bevacizumab. Mater Sci Eng C [Internet]. 2019;98:843–60. Available from: http://www.sciencedirect.com/science/article/pii/S092849311832263X

83. Zhu R, Wang Z, Liang P, He X, Zhuang X, Huang R, et al. Efficient VEGF targeting delivery of DOX using Bevacizumab conjugated SiO2@LDH for anti-neuroblastoma therapy. Acta Biomater [Internet]. 2017;63:163–80. Available from: http://www.sciencedirect.com/science/article/pii/S174270611730572X

84. Zhang X, Wang C, Wang J, Hu Q, Langworthy B, Ye Y, et al. PD-1 Blockade Cellular Vesicles for Cancer Immunotherapy. Adv Mater [Internet]. 2018;30(22):1707112. Available from: https://doi.org/10.1002/adma.201707112

85. Li Y, Fang M, Zhang J, Wang J, Song Y, Shi J, et al. Hydrogel dual delivered celecoxib and anti-PD-1 synergistically improve antitumor immunity. Oncoimmunology [Internet]. 2015 Aug 12;5(2):e1074374–e1074374. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27057439

86. Wang C, Ye Y, Hochu GM, Sadeghifar H, Gu Z. Enhanced Cancer Immunotherapy by Microneedle Patch-Assisted Delivery of Anti-PD1 Antibody. Nano Lett [Internet]. 2016;16(4):2334–40. Available from: https://doi.org/10.1021/acs.nanolett.5b05030

87. Wang C, Sun W, Ye Y, Hu Q, Bomba HN, Gu Z. In situ activation of platelets with checkpoint inhibitors for post-surgical cancer immunotherapy. Nat Biomed Eng [Internet]. 2017;1:11. Available from: http://dx.doi.org/10.1038/s41551-016-0011

88. Chen Q, Wang C, Chen G, Hu Q, Gu Z. Delivery Strategies for Immune Checkpoint Blockade. Adv Healthc Mater [Internet]. 2018 Oct 1;7(20):1800424. Available from: https://doi.org/10.1002/adhm.201800424

89. Untch M, Jackisch C, Schneeweiss A, Conrad B, Aktas B, Denkert C, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. Lancet Oncol [Internet]. 2016 Mar 1;17(3):345–56. Available from: https://doi.org/10.1016/S1470-2045(15)00542-2

90. O'Brien S, Schiller G, Lister J, Damon L, Goldberg S, Aulitzky W, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. J Clin Oncol [Internet]. 2012/11/19. 2013 Feb 20;31(6):676–83. Available from:

https://pubmed.ncbi.nlm.nih.gov/23169518

91. Hendricks BK, Cohen-Gadol AA, Miller JC. Novel delivery methods bypassing the blood-brain and blood-tumor barriers. Neurosurg Focus [Internet]. 2015 Mar;38(3):E10–E10. Available from: https://pubmed.ncbi.nlm.nih.gov/25727219

92. Manabe T, Okino H, Maeyama R, Mizumoto K, Tanaka M, Matsuda T. New infusion device for trans-tissue, sustained local delivery of anticancer agent to surgically resected tissue: Potential use for suppression of local recurrence of pancreatic cancer. J Biomed Mater Res Part B Appl Biomater [Internet]. 2005 Apr 1;73B(1):203–7. Available from: https://doi.org/10.1002/jbm.b.30186

93. Krukiewicz K, Zak JK. Biomaterial-based regional chemotherapy: Local anticancer drug delivery to enhance chemotherapy and minimize its side-effects. Mater Sci Eng C [Internet]. 2016;62:927–42. Available from: http://www.sciencedirect.com/science/article/pii/S0928493116300625

94. Sartor O. Eligard: leuprolide acetate in a novel sustained-release delivery system. Urology [Internet]. 2003;61(2, Supplement):25–31. Available from: http://www.sciencedirect.com/science/article/pii/S0090429502023968

95. FOWLER JE, GOTTESMAN JE, REID CF, ANDRIOLE GL, SOLOWAY MS. SAFETY AND EFFICACY OF AN IMPLANTABLE LEUPROLIDE DELIVERY SYSTEM IN PATIENTS WITH ADVANCED PROSTATE CANCER. J Urol [Internet]. 2000;164(3, Part 1):730–4. Available from: http://www.sciencedirect.com/science/article/pii/S0022534705672916

96. Vellimana AK, Recinos VR, Hwang L, Fowers KD, Li KW, Zhang Y, et al. Combination of paclitaxel thermal gel depot with temozolomide and radiotherapy significantly prolongs survival in an experimental rodent glioma model. J Neurooncol [Internet]. 2013;111(3):229–36. Available from: https://doi.org/10.1007/s11060-012-1014-1

97. Tyler B, Fowers KD, Li KW, Recinos VR, Caplan JM, Hdeib A, et al. A thermal gel depot for local delivery of paclitaxel to treat experimental brain tumors in rats. J Neurosurg [Internet]. 2010 Aug;113(2):210–7. Available from: https://pubmed.ncbi.nlm.nih.gov/20001591

98. Celikoğlu F, Celikoğlu SI. Intratumoural chemotherapy with 5-fluorouracil for palliation of bronchial cancer in patients with severe airway obstruction. J Pharm Pharmacol [Internet]. 2003 Oct;55(10):1441–8. Available from: https://pubmed.ncbi.nlm.nih.gov/14607028

99. Jabbardarjani H. ENDOBRONCHIAL CHEMOTHERAPY IN MALIGNANT LESIONS OF THE LUNG: REPORT OF 5 YEARS↓ EXPERIENCE. Chest [Internet]. 2008 Oct 1;134(4):97P. Available from: https://doi.org/10.1378/chest.134.4_MeetingAbstracts.p97001

100. Jabbardarjani H, Kharabian S, Masjedi MR. Endobronchial Chemotherapy in Malignant Airway Lesions of the Lung: Report of 3 Years Experience. J Bronchology Interv Pulmonol [Internet]. 2007;14(4). Available from: https://journals.lww.com/bronchology/Fulltext/2007/10000/Endobronchial_Chemotherapy_in_Malignant_Airway.6.aspx

101. da Silva GR, da Silva-Cunha A, Behar-Cohen F, Ayres E, Oréfice RL. Biodegradation of polyurethanes and nanocomposites to non-cytotoxic degradation products. Polym Degrad Stab [Internet]. 2010;95(4):491–9. Available from: http://www.sciencedirect.com/science/article/pii/S014139101000011X

102. Chen Y, Wang R, Zhou J, Fan H, Shi B. On-demand drug delivery from temperature-responsive polyurethane membrane. React Funct Polym [Internet]. 2011;71(4):525–35. Available from: http://www.sciencedirect.com/science/article/pii/S1381514811000241

103. Kang S-G, Lee SC, Choi SH, Park S, Jeong S, Lee DH, et al. Paclitaxel-polyurethane film for anti-cancer drug delivery: Film characterization and preliminary in vivo study. Macromol Res [Internet]. 2010;18(7):680–5. Available from: https://doi.org/10.1007/s13233-010-0715-6

104. Mazzucchelli S, Bellini M, Fiandra L, Truffi M, Rizzuto MA, Sorrentino L, et al. Nanometronomic treatment of 4T1 breast cancer with nanocaged doxorubicin prevents drug resistance and circumvents cardiotoxicity. Oncotarget. 2017 Jan;8(5):8383–96.

105. Toffoli G, Hadla M, Corona G, Caligiuri I, Palazzolo S, Semeraro S, et al. Exosomal doxorubicin reduces the cardiac toxicity of doxorubicin. Nanomedicine (Lond). 2015 Oct;10(19):2963–71.

106. Bikram M, West JL. Thermo-responsive systems for controlled drug delivery. Expert Opin Drug Deliv [Internet]. 2008;5(10):1077–91. Available from: https://doi.org/10.1517/17425247.5.10.1077

107. Karimi M, Sahandi Zangabad P, Ghasemi A, Amiri M, Bahrami M, Malekzad H, et al. Temperature-Responsive Smart Nanocarriers for Delivery Of Therapeutic Agents: Applications and Recent Advances. ACS Appl Mater Interfaces [Internet]. 2016 Aug 24;8(33):21107–33. Available from: https://doi.org/10.1021/acsami.6b00371

108. Calejo MT, Sande SA, Nyström B. Thermoresponsive polymers as gene and drug delivery vectors: architecture and mechanism of action. Expert Opin Drug Deliv [Internet]. 2013;10(12):1669–86. Available from: https://doi.org/10.1517/17425247.2013.846906

109. Cao D, Zhang X, Akabar MD, Luo Y, Wu H, Ke X, et al. Liposomal doxorubicin loaded PLGA-PEG-PLGA based thermogel for sustained local drug delivery for the treatment of breast cancer. Artif Cells, Nanomedicine, Biotechnol [Internet]. 2019;47(1):181–91. Available from: https://doi.org/10.1080/21691401.2018.1548470

110. Dewhirst MW, Landon CD, Hofmann CL, Stauffer PR. Novel approaches to treatment of hepatocellular carcinoma and hepatic metastases using thermal ablation and thermosensitive liposomes. Surg Oncol Clin N Am [Internet]. 2013 Jul;22(3):545—561. Available from: https://europepmc.org/articles/PMC3738918

111. Pham SH, Choi Y, Choi J. Stimuli-Responsive Nanomaterials for Application in Antitumor Therapy and Drug Delivery. Pharmaceutics [Internet]. 2020;12(7). Available from: https://www.mdpi.com/1999-4923/12/7/630

112. Hayashi K, Nakamura M, Miki H, Ozaki S, Abe M, Matsumoto T, et al. Magnetically Responsive Smart Nanoparticles for Cancer Treatment with a Combination of Magnetic Hyperthermia and Remote-Control Drug Release. Theranostics [Internet]. 2014;4:834–44. Available from: https://www.thno.org/v04p0834.htm

113. Alirezaie Alavijeh A, Barati M, Barati M, Abbasi Dehkordi H. The Potential of Magnetic Nanoparticles for Diagnosis and Treatment of Cancer Based on Body Magnetic Field and Organ-on-the-Chip. Adv Pharm Bull [Internet]. 2019;9(3):360–73. Available from: https://apb.tbzmed.ac.ir/Article/apb-25289

114. Albinali KE, Zagho MM, Deng Y, Elzatahry AA. A perspective on magnetic core-shell carriers for responsive and targeted drug delivery systems. Int J Nanomedicine [Internet]. 2019 Mar 6;14:1707–23.

Available from: https://pubmed.ncbi.nlm.nih.gov/30880975

115. Wang H, Yi J, Mukherjee S, Banerjee P, Zhou S. Magnetic/NIR-thermally responsive hybrid nanogels for optical temperature sensing{,} tumor cell imaging and triggered drug release. Nanoscale [Internet]. 2014;6(21):13001–11. Available from: http://dx.doi.org/10.1039/C4NR03748K

116. Hua M-Y, Liu H-L, Yang H-W, Chen P-Y, Tsai R-Y, Huang C-Y, et al. The effectiveness of a magnetic nanoparticle-based delivery system for BCNU in the treatment of gliomas. Biomaterials [Internet]. 2011;32(2):516–27. Available from: http://www.sciencedirect.com/science/article/pii/S0142961210012627

117. Boissenot T, Bordat A, Fattal E, Tsapis N. Ultrasound-triggered drug delivery for cancer treatment using drug delivery systems: From theoretical considerations to practical applications. J Control Release. 2016 Nov;241:144–63.

118. Pitt WG, Husseini GA, Staples BJ. Ultrasonic drug delivery – a general review. Expert Opin Drug Deliv [Internet]. 2004;1(1):37–56. Available from: https://doi.org/10.1517/17425247.1.1.37

119. Tharkar P, Varanasi R, Wong WSF, Jin CT, Chrzanowski W. Nano-Enhanced Drug Delivery and Therapeutic Ultrasound for Cancer Treatment and Beyond. Front Bioeng Biotechnol [Internet]. 2019;7:324. Available from: https://www.frontiersin.org/article/10.3389/fbioe.2019.00324

120. Mullick Chowdhury Sayan Lee Taehwa WJK. Ultrasound-guided drug delivery in cancer. Ultrasonography [Internet]. 2017;36(3):171–84. Available from: http://www.e-ultrasonography.org/journal/view.php?number=185

121. O'Neill HS, Gallagher LB, O'Sullivan J, Whyte W, Curley C, Dolan E, et al. Biomaterial-Enhanced Cell and Drug Delivery: Lessons Learned in the Cardiac Field and Future Perspectives. Adv Mater [Internet]. 2016;28(27):5648–61. Available from: http://dx.doi.org/10.1002/adma.201505349

122. Singla DK. Akt—mTOR Pathway Inhibits Apoptosis and Fibrosis in Doxorubicin-Induced Cardiotoxicity following Embryonic Stem Cell Transplantation. Cell Transplant [Internet]. 2015;24(6):1031–42. Available from: https://doi.org/10.3727/096368914X679200

123. Bolli R, Perin EC, Willerson JT, Yang PC, Traverse JH, Henry TD, et al. Allogeneic Mesenchymal Cell Therapy in Anthracycline-Induced Cardiomyopathy Heart Failure Patients: The CCTRN SENECA Trial. JACC CardioOncology [Internet]. 2020; Available from: http://www.sciencedirect.com/science/article/pii/S2666087320302143

124. European Medicines Agency. Questions and answers on the review of dexrazoxane-containing medicines, powder for solution for infusion, 500 mg. Outcome of a procedure under Article 31 of Directive 2001/83/EC as amended. 2011; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Dexrazoxane_31/WC500108011.pdf

125. Tebbi CK, London WB, Friedman D, Villaluna D, De Alarcon PA, Constine LS, et al. Dexrazoxane-Associated Risk for Acute Myeloid Leukemia/Myelodysplastic Syndrome and Other Secondary Malignancies in Pediatric Hodgkin's Disease. J Clin Oncol [Internet]. 2007 Feb 10;25(5):493–500. Available from: https://doi.org/10.1200/JCO.2005.02.3879

126. Garcia JR, Campbell PF, Kumar G, Langberg JJ, Cesar L, Wang L, et al. A Minimally Invasive,

Translational Method to Deliver Hydrogels to the Heart Through the Pericardial Space. JACC Basic to Transl Sci [Internet]. 2017 Oct 4;2(5):601–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30062173

127. R. GJ, F. CP, Gautam K, J. LJ, Liliana C, N. DJ, et al. Minimally Invasive Delivery of Hydrogel-Encapsulated Amiodarone to the Epicardium Reduces Atrial Fibrillation. Circ Arrhythmia Electrophysiol [Internet]. 2018 May 1;11(5):e006408. Available from: https://doi.org/10.1161/CIRCEP.118.006408

128. Whyte W, Roche ET, Varela CE, Mendez K, Islam S, O'Neill H, et al. Sustained release of targeted cardiac therapy with a replenishable implanted epicardial reservoir. Nat Biomed Eng [Internet]. 2018;2(6):416–28. Available from: http://www.nature.com/articles/s41551-018-0247-5

129. Zordoky BNM, Robertson IM, Dyck JRB. Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases. Biochim Biophys Acta - Mol Basis Dis [Internet]. 2015;1852(6):1155–77. Available from: http://www.sciencedirect.com/science/article/pii/S0925443914003226

130. Tatlidede E, Şehirli Ö, Velioğlu-Öğünç A, Çetinel Ş, Yeğen BÇ, Yarat A, et al. Resveratrol treatment protects against doxorubicin-induced cardiotoxicity by alleviating oxidative damage. Free Radic Res [Internet]. 2009 Jan 1;43(3):195–205. Available from: https://doi.org/10.1080/10715760802673008

131. Xu Q, Si L-Y. Resveratrol role in cardiovascular and metabolic health and potential mechanisms of action. Nutr Res [Internet]. 2012;32(9):648–58. Available from: http://www.sciencedirect.com/science/article/pii/S0271531712001492

132. Gu J, Hu W, Song Z, Chen Y, Zhang D, Wang C. Resveratrol-induced autophagy promotes survival and attenuates doxorubicin-induced cardiotoxicity. Int Immunopharmacol [Internet]. 2016;32:1–7. Available from: http://www.sciencedirect.com/science/article/pii/S1567576916300030

133. Xu X, Chen K, Kobayashi S, Timm D, Liang Q. Resveratrol attenuates doxorubicin-induced cardiomyocyte death via inhibition of p70 S6 kinase 1-mediated autophagy. J Pharmacol Exp Ther [Internet]. 2011/12/30. 2012 Apr;341(1):183–95. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22209892

134. Gu J, Fan Y, Zhang H, Pan J, Yu J, Zhang J, et al. Resveratrol suppresses doxorubicin-induced cardiotoxicity by disrupting E2F1 mediated autophagy inhibition and apoptosis promotion. Biochem Pharmacol [Internet]. 2018;150:202–13. Available from: http://www.sciencedirect.com/science/article/pii/S0006295218300820

135. Osman A-MM, Al-Harthi SE, AlArabi OM, Elshal MF, Ramadan WS, Alaama MN, et al. Chemosensetizing and cardioprotective effects of resveratrol in doxorubicin- treated animals. Cancer Cell Int [Internet]. 2013 May 28;13:52. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23714221

136. Zhang L, Zhu K, Zeng H, Zhang J, Pu Y, Wang Z, et al. Resveratrol solid lipid nanoparticles to trigger credible inhibition of doxorubicin cardiotoxicity. Int J Nanomedicine [Internet]. 2019 Jul 31;14:6061–71. Available from: https://pubmed.ncbi.nlm.nih.gov/31534336

137. De Angelis A, Piegari E, Cappetta D, Russo R, Esposito G, Ciuffreda LP, et al. SIRT1 activation rescues doxorubicin-induced loss of functional competence of human cardiac progenitor cells. Int J Cardiol [Internet]. 2015 Jun 15;189:30–44. Available from: https://doi.org/10.1016/j.ijcard.2015.03.438

138. Brookins Danz ED, Skramsted J, Henry N, Bennett JA, Keller RS. Resveratrol prevents doxorubicin

cardiotoxicity through mitochondrial stabilization and the Sirt1 pathway. Free Radic Biol Med [Internet]. 2009;46(12):1589–97. Available from: http://www.sciencedirect.com/science/article/pii/S0891584909001543

139. Carlson LJ, Cote B, Alani AW, Rao DA. Polymeric micellar co-delivery of resveratrol and curcumin to mitigate in vitro doxorubicin-induced cardiotoxicity. J Pharm Sci. 2014 Aug;103(8):2315–22.