The Cardiotoxicity Caused by Anticancer Drugs

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Abstract- ***Chemotherapy and targeted therapy have greatly enhanced the prognosis of patients with oncology. Nevertheless, such antineoplastic therapies can also cause unwanted cardiovascular effects, which can be followed by acute or late-onset cardiac dysfunction. These frequent cardiovascular complications, usually called cardiotoxicity, not only can necessitate the adjustment, interruption, or withdrawal of life-saving antineoplastic treatments, with the risk of diminishing their effectiveness, but also can significantly influence the quality of life and survival, irrespective of the oncological prognosis. The development of cardiotoxicity can be dependent on the class, dose, route, and duration of administration of anticancer agents, as well as on individual risk factors. Notably, the cardiotoxic side effects can be reversible, if cardiac function is resumed upon termination of the treatment, or irreversible, in that it is associated with injury and loss of cardiac muscle cells. Subclinical myocardial dysfunction caused by anticancer treatments may also later progress into symptomatic congestive heart failure. Thus, there is a pressing requirement for cardioprotective therapy to decrease the clinical and subclinical cardiotoxicity onset and progression and the acute or chronic manifestation of cardiac injuries. Here in, we review the information about cellular and molecular mechanisms underlying the development of cardiotoxicity from standard classes of chemotherapeutic and targeted therapy agents. In addition, we outline and discuss existing and future approaches to managing the cardiotoxic side effects and cardioprotective preventive measures that would be beneficial to flank anticancer therapies.***

Indexed Terms- ***Anticancer, Chemotherapy Cardiotoxicity, Dose***

I. INTRODUCTION

There are a continuum of harmful effects to the heart known as cardiotoxicity-explored the following the main representatives of arrhythmias (like torsades de pointes produced: drugs prolonging the QT interval), elevated blood pressure, myocardial ischemia, thrombosis, or issues with the heart's ability to contract or relax (systolic and diastolic dysfunction). Consistent with these issues lies fatal cardiovascular safety as the biggest challenge related to the regulatory authorities and the physicians to protect the patients. For regulators, QT prolongation; commonly the blocking of the hERG potassium channels, is the primary issue that caused most drugs either to be impactfully withdrawn or be overridden with new labeling reforms during the last decade. Current guidelines recommend stringent early-stage testing in order to detect the risk at a much earlier stage of drug development. Nevertheless, this review is concentrating on another angle that relates to cardiotoxicity-damage done to the heart after treatment with anticancer drugs. Most cancers have the side effect of reducing LVEF and CHF. Earlier, the two taxonian drugs associated with this problem were proven to be anthracyclines, and the damage to the heart was dependent on the accumulation dose. There appears to be no group agreement about what is the best means to predict, prevent, and monitor cardiotoxicity due to chemotherapy, since many trials are aimed at finding an answer to this. The situation has been even further confounded with the emergence of drugs that targeted either tyrosine kinases or tumor receptors, which displayed unforeseen cardiovascular side effects. The combination of relatively older chemotherapy drugs such as anthracyclines with trastuzumab has led to shocking figures of heart-related issues. The scenario has put forward both researchers and clinicians on how one should best control this problem. It falls back to two aspects which the researchers need to review more under the ambit of the automated framework of this review: (1) the molecular mechanisms in cytotoxic cardiotoxicity and (2) the challenges in reducing these risks in clinical practice through molecular biology-based drug and intervention design.(Therapy n.d.)

What Exactly Does Cardiotoxicity Mean?

The National Cancer Institute defines cardiotoxicity in very extensive terms as “toxicity that influences the coronary coronary heart” .However, even though it is appreciably recognized that severa most cancers chemotherapeutics adversely have an impact at the coronary coronary coronary heart and the vascular gadget, and that a developing extensive sort of medical trials (registered at www.Clinicaltrials.Gov) in the interim are analyzing lengthy-time period thing results of anticancer remedy, along with cardiovascular activities, a easy statistics of what cardiotoxicity is and the way anticancer remedy stresses the cardiovascular tool is lacking. One of the maximum correct scientific definitions of cardiotoxicity has been formulated with the resource of the cardiac review and assessment committee supervising trastuzumab scientific trials, which defined drug-associated cardiotoxicity as one or greater of the subsequent: 1) cardiomyopathy in phrases of a discount in left ventricular ejection fraction (LVEF), both international or more intense inside the septum; 2) signs and signs and symptoms associated with coronary heart failure (HF); 3) symptoms related to HF, which consist of S3 gallop, tachycardia, or each; 4) cut fee in LVEF from baseline that is within the variety of much much less than or same to 5% to lots lots much less than 55% with accompanying symptoms and symptoms or symptoms and signs and symptoms and symptoms of HF, or a discount in LVEF in the fashion of equal to or more than 10% to lots less than fifty five%, with out accompanying signs and symptoms and symptoms or symptoms and signs and signs (7). This definition does now not embody subclinical cardiovascular damage that would stand up early in reaction to 3 chemotherapeutic stores; as a consequence (Albini et al. 2010)

DRUGS	CARDIOTOXICITY	PREVENTION
Anthracyclines	LV dysfunction / HP	Liposomal Anthracycline Dexrazoxane
HER2 inhibitors	LV dysfunction	ACEI/ARB β-blockers
Immune checkpoint inhibitors	Immune myocardiates	Haemodynamically unstable -1000 mg of methylprednisolone daily
VEGF inhibitors and Multi-Targeted Kinase Inhibitors	Hypertension LV dysfunction Vascular toxicity	Daily Home blood pressure monitoring during the first treatment cycle, and every 2-3 weeks thereafter for patients treated with VEGFL BP> 140/90 mm Hg receive antihypertensive therapy
TKIs and Anti BCR-ABL Agents	Cardic dysfunction QTc prolongation	Discontinution of chemotherapy Aspirin and statin
Taxanes	Bradycardia LV dysfunction Ischemia	Cortisol Antihistamines
Flurouracil	Coronary spasms/ Ischemia	Discontinuation of chemotherapy Calcium CHANNEL Blockers or Nitrates

Oncology patients now have a far better prognosis because to chemotherapy and targeted treatments. Acute or delayed onset of cardiac dysfunction could result from these antineoplastic therapies' potential to cause negative cardiovascular side effects. Regardless of the oncological prognosis, these frequent cardiovascular complications—also known as cardiotoxicity—can have a significant impact on quality of life and overall survival. They may also necessitate the modification, suspension, or withdrawal of life-saving antitumor therapies, which carries the risk of decreasing their efficacy. The class, dosage, mode, and length of anticancer medication administration, in addition to personal risk factors, may all affect when cardiotoxicity first appears. Crucially, if heart function returns after stopping the

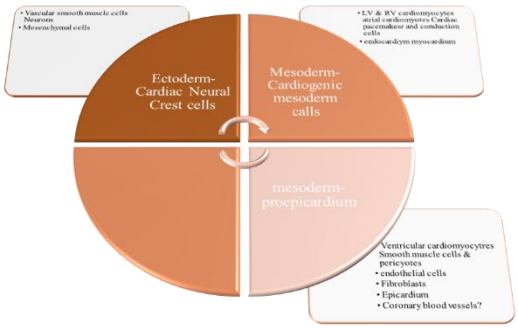
treatment, the cardiotoxic side effects may be reversible; otherwise, they may be irreversible.(No Title n.d.)

Cardiotoxicity caused by anti-cancer drugs:
The deadliest illness in the world today is cancer. Over 800,000 of the 3.45 million new cases of cancer, excluding non-melanoma skin cancers, and 1.75 million deaths from cancer reported in Europe in 2012 were attributable to breast and prostate cancers. The majority of cancer drugs target tumor-related angiogenesis, neoplastic transformation, invasion, metastasis, and cell proliferation. Theoretically, because targeted therapy would spare healthy cells, it would be better tolerated. Unfortunately, the ideal anti-cancer medication has not yet been found, and non-cancer cells are still severely affected.[2]
Generally pharmacologically, anti-cancer drugs that are classified with chemotherapy.
(Reis-mendes *et al*. 2016)

II. CARDIAC DEVELOPMENT AND CARDIAC CELL PHYSIOLOGY

The cardiovascular system is the first organ to start functioning in human fetal development. Three germ layers are established during gastrulation: a dorsal ectoderm, a ventral endoderm, and a mesoderm layer that is derived from the single-layered blastula. Myocardial progenitor cells differentiate from the mesoderm germ layer into cardiomyocytes and non-cardiomyocytes, endothelial cells, postnatal cardiac progenitor cells, and vascular smooth muscle cells. These then migrate and merge to form a bilaterally cardiogenic plate that is made up of two endocardial tubes. Upon the latter two joining, a primary heart tube is formed. The endocardial tubes are products of cardiac embryogenesis and, in a cellular context, of the germ layer mesoderm, differentiating to form mesothelium, endothelium, and myocardium in order to be able to form the construction of both cardiomyocytes and non-cardiomyocytes. The main heart tube consists of an innermost layer referred to as an endocardial layer.

(Koukorava et al. 2024)



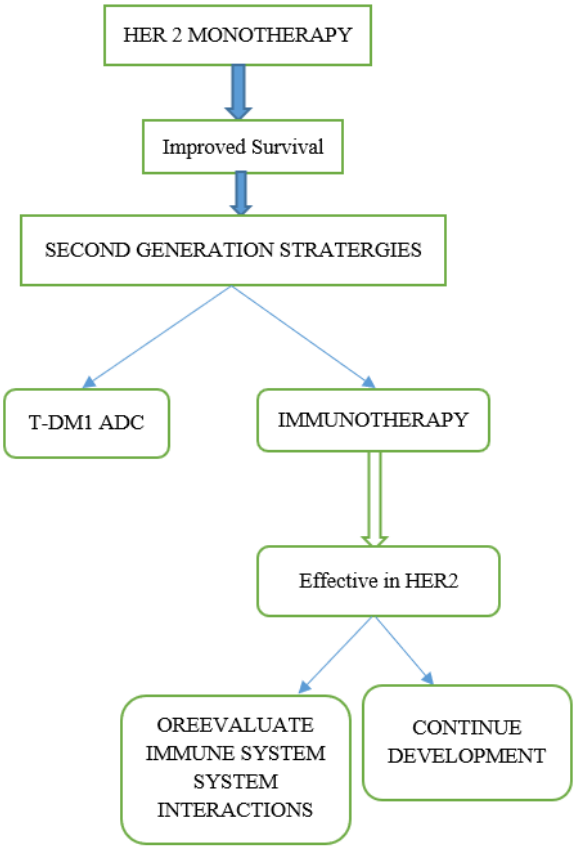
Anticancer Drugs:
Anthracyclines-Induced Cardiotoxicity Scientist H. Brockmann first named anthracyclines in 1950. Since then, a number of anthracyclines, including doxorubicin and daunorubicin, have been discovered and applied to treat a variety of cancers.43 Clinicians have increasingly become more aware of the significant cardiac adverse effects associated with the extensive use of anthracyclines. Anthracycline's CTRCD is separated into two categories: early cardiotoxicity and late cardiotoxicity. Early acute and early chronic cardiotoxicity are the two categories of early cardiotoxicity. Early chronic cardiotoxicity usually happens within a year following anthracycline treatment, but early acute cardiotoxicity usually happens during or a few days to weeks after anthracycline treatment and is primarily expressed as arrhythmias. Overview of Anticancer Drugs That Cause Cardiotoxicity Reference for Cardiotoxicity Prevention Anthracyclines and HF/LV dysfunction [HER2 Inhibitors] Liposomal anthracycline Dexrazoxane

(Gao *et al*. 2024)(Design 2024)
Because anthracyclines can impede topoisomerase activity, they can stop cells from proliferating or repairing. There are two main types of topoisomerase-2 (Top2): Top2β is found in all mammalian cells, including cardiomyocytes, but Top2α is only produced in proliferating cells and is thought to be the primary target of doxorubicin's anti-cancer activities. Doxorubicin binds to both isoforms non-selectively because of their identical sequences. DNA is intercalated by doxorubicin, which also stabilizes the Top2 cleavage complex and prevents the advancement

of the DNA replication fork . The cleavage complex causes Top2β to be degraded by proteases when the replication machinery is unable to replicate DNA. This reveals double-stranded DNA breaks and starts a series of p53-mediated processes, including intrinsic apoptosis and mitochondrial malfunction . This is in line with research showing that Top2β deletion(Kwok and Nolan 2023)

III. MONOCLONAL ANTIBODIES ANTI-HER2

Monotherapy with antibodies against HER 2 has greatly increased the survival improvement of ERBB2 positive (HER 2+) breast cancer patients, either in the loco-regional advanced, limited disease, or metastatic settings. Second-generation treatment strategies, including the antibody drug conjugate (ADC) T-DM1, deliver the-another argument-for continued consideration of HER2 as a strong target for future therapeutics development. Immunotherapy has successfully emerged in many solid tumors as an effective category of therapies using monoclonal antibodies to modulate the PD-1/PD-L1 checkpoint. However, these agents have shown no clinically meaningful responses in unselected patients, especially in those who are HER2 positive. Taking into account these displays of clinical and preclinical evidence, the more intricate relations between the immune system's two parts, innate and adaptive, must be weighed in future therapeutic endeavors with clinically relevant



(Costa and Czerniecki 2020)

Currently, three anti-human epidermal growth factor receptor (HER2) monoclonal antibodies are approved for use; trastuzumab, pertuzumab and margetuximab. Trastuzumab is a humanised monoclonal antibody that targets the extracellular segment of the HER2, (ErbB2) family which is a type of transmembrane receptor tyrosine kinase, gastric cancer, and twenty percent of all breast cancer. Cancers that overexpress HER2 account for 20% of all breast and gastric cancers , and trastuzumab is the recommended firstline treatment. Clinically, trastuzumab treatment alone may cause reduced LV ejection fraction but typically does not cause arrhythmias. However, they are worsened when allied with anthracyclines or other chemotherapies like in metastatic HER2 positive breast cancers Also, there is a serious interaction because trastuzumab cannot be used at the same time as anthracycline but must be used sequentially with it and other factors such as background cardiac risk factors as well as patient specific tailored cardiac assessment should be taken into account (Kwok and Nolan 2023)

Given that ligands do not bind specifically, it has been noted that HER2 activation can also occur through homo and hetero-dimerization and subsequent autophosphorylation of tyrosine kinase residues on its cytoplasmic domain. The overexpression using HER2 leads to the abnormal breast cancer cells that do not respond have uncontrolled activation of the three major(Kwok and Nolan 2023)

Trastuzumab

TRZ, the first anti-HER2 monoclonal antibody, was initially authorized by the Food and Drug Administration in 1998 to treat breast tumors that overexpress HER2. In HER2-overexpressing cancer cells, TRZ functions by attaching to HER2 extracellular domain IV and disabling ligand-independent carcinogenic HER2/HER3 interactions. By impairing cells' capacity to engage signal transduction pathways for maintaining the integrity and function of cardiomyocytes and, most importantly, cardioprotective responses against harmful stimuli, interference with HER2/NRG-1 signaling contributes significantly to the development of deleterious cardiac consequences. TRZ cardiotoxicity has been linked to mitochondrial malfunction decreased contractile and metabolic characteristics and suppression of autophagy [according to data from both in vitro and in vivo investigations.(Chianca et al. 2023)

How is this medication different from others chemotherapy medications? One of the growth-promoting proteins of a tyrosine kinase receptor is HER2, and this is present on the surface of some cancer cells, associated with aggressive disease. The protein is overexpressed in about 1 in 5 breast tumors. Cancer cells from most breast tumors are checked using either immunohistochemistry (IHC) or fluorescence in situ hybridization to see whether they are HER2-positive (FISH). There are still quite a few requests for HER2-expressing metastatic breast cancer at this time. In fact, as of date, there is still no set standard of care in HER2-positive cancers post-treatment with trastuzumab, pertuzumab, and T-DM1, and the majority of these cancers have reached a point wherein none of the currently available drugs targeting HER2 can provide continued control over the disease. More importantly, none of the anti-HER2 drugs have been proposed for HER2 low-expression cancers. These unmet needs provide an opportunity for a new drug called ENHERTU to enter the market and dominate the market. ENHERTU was designed as a targeted therapy, an ADC, to be unlike conventional chemotherapies.(Delveinsight 2023)

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The Trastuzumab, a humanized IgG1 monoclonal antibody, is custom-made to the extracellular section of the HER-2 receptors (ErbB-2) which is the main feature of this biologic. The HER-2 receptor was in the past only known because of its extracellular region, transmembrane domain, and an inner cytoplasmic domain which in combination with the growth factor of the tyrosine kinase enzyme is involved in the phosphorylation of some cytoplasmic proteins. The receptor HER-2 is additionally formed by other less characterized domains. This is needed to avoid decay and the activation of the receptor's extracellular site through the binding of trastuzumab to the complex of HER-2 immune cells, it is so that the HER-2 dimerization effect ceases. The cells of the immune system also play an active role in the self-destruction of cancer cells, which leads to the killing of the tumor

cells and therefore the HER-2 internalization () is acco. This is what the immune cells are doing, these cells are getting closer to the tumor cells; at the same, they are also giving the apoptotic signal and the HER-2 is also internalized via this procedure, which results in a well-tolerated therapeutic effect.(Raab and Eiermann 2000)

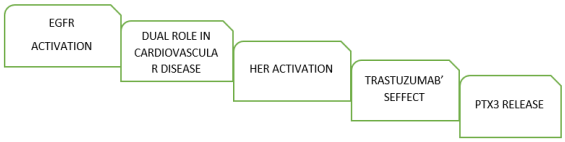
HER2 inhibitor mechanism.

Her2 membrane tyrosine kinase receptor family consists of four members, HER1 to HER4. HER2 is an orphan ligand receptor that is expressed in many human tumors and is highly significant in 25–30% of breast cancers. HER2 improves the signal sent by other receptors of his family to form heterodimer. This major role of HER2 in the propagation of the signal transmission network has brought about anti-GE2-MAB as treatment to cancer. Notably, a humanized monoclonal antibody, trastuzumab (Herceptin) that is utilized as the major anticancer medication used for treatment against women carrying overexpression breast cancer and who harbor overexpressing cells in human breast cancer. Downmodulation of the HER2 receptor leads to the inhibition of the two main signaling pathways: ras-Raf-MAPK and PI3K/Akt. Additionally, the treatment causes the formation of the p27/Cdk2 complex that prevents the cell cycle progression. Furthermore, modulation of down-regulated receptors by up-regulated antibodies is also inhibited by Trastuzumab. This might explain some antitumor effects in certain cancers. The one disadvantage of trastuzumab is that the drug's greatest efficacy is demonstrated in breast cancers with the most intense HER2 overexpression or HER2 gene amplification. Nonetheless, there exist many subsets of breast cancers, and numerous tumors with low or intermediate levels of HER2 expression. In such tumors, HER2 functions more like its favourite cocker spaniel, forming heterodimers with HER2 (EGFR), HER3, or HER4. This is being addressed by the development of a humanized monoclonal antibody that targets the co-receptor role of HER2: 2C4, binds to a distinct HER2 ectodomain epitope in comparison with trastuzumab and(Albanell et al. 2003) sterically prevents the formation of heterodimers of HER2 with other HER receptors. Therefore, both HER2-low and -high cells exhibit inhibited HER2-based heterodimeric signaling. 2C4 has been reported to show antitumor activity in numerous models of breast and prostate cancers in vitro and in vivo. Therefore, 2C4 might be useful in the treatment of a wide range of solid tumors.(Albanell et al. 2003)

ERBB2 (also known as HER2) is a member of the epidermal factor of the growing receiver of the person who also includes ERBB1 (EGFR), ERBB3, and ERBB4. HER2 cannot train diplomatic surgery that depends on ligand independently to activate low signals, and to form other proteins and heterodimar from the family to satisfy the function, EGFR / HER2. / HER3 complexes are the most important for physiological functions and are most related to tumors. Studies related to cardiacity and mechanisms that interfere with some routes such as New Leglin 1 (NRG1), oxidative stress, and felloptosis are always limited, and need more attention. The activation of the NRG1-ERBB4 signaling path, as indicated, stimulates the mature division of cardiomyocytes. Physiological function. , interfering in the NRG1-ERBB4-ERBB2 axis in the myocardium and proteinquinase activated by mitogens (MAPK) and phosphatidydilinositol-3-kinase (PI3K), leading to an important role to the myocardium. In heart failure, which is played. This study suggests that drugs aimed at HER2 can cause cardiotoxicity, disturbing the intracellular antioxidant system, which leads to an increase in the production of active oxygen forms. The ATP content and the reduction in GPX expression and the GSH / GSSG ratio in H9C2 cells. These changes were reversed by ferrostatin-1, a ferroptosis inhibitor, and this study demonstrated that ferroptosis is closely associated with HER2 inhibitor-induced cardiotoxicity.

EGFR is the first member of the HER family, which is essential for cardiac growth and development, but plays a dual role in cardiovascular disease. Upon ligand binding, EGFR is converted from an inactive monomer to an active homodimer or heterodimer with other ErbB family members (ErbB2/HER2/neu, ErbB3, and ErbB4) to activate downstream signaling.105 Studies have shown that EGFR activation can regulate vasoconstriction or diastole, resulting in either a hypertensive or antihypertensive effect. This depends on whether EGFR has a significant impact on the substance content that expands endogenous vessels or whether or not smooth muscles are controlled. The activation of EGFR

promotes traces of collateral and promotes the formation of useful effects, but in diabetes mice, EGFR increases blood vessels and deteriorates due to retinal edema. In addition to the antibodies that block the EGFR, in the repetitive animal model, the number of blood vascular smooth muscle growth and endothelium formation decreased after the balloon lesion. Increase the level of CAMP of muscle cells and the sublimation of the Heart muscle. However, EGFR leads to blood vessel remodeling and medium, and



thus brings the heart remodeling, which increases the expression of EGFR, leading to cardiomyophagia and blood vessels. The harmful effect of activating EGFR on the heart may be due to the activation of AKT signal communication. Route PTEN / AKT / FOXO3A, method, mitochondrial dysfunction trigger and cardiac. The activation of HER2 inhibits the decomposition of rapid endocaits and EGFR, extends the signaling of phosphorylation downstream, and promotes cell growth and growth. As a double inhibitor of EGFR and HER2, Lapachinib blocks the excretion of doxolbicin by inhibiting the protein of ABC emission transportation that depends on ATP is XU ET AL. It was identified by. This study demonstrated that HER2 is still abundantly expressed in adult mouse cardiac capillary endothelial cells (VECs) and that exposure of cardiomyocytes to trastuzumab-treated VEC medium caused impaired cardiomyocyte contraction.PTX3 is the only protein released by VECs and therefore plays an important role in endothelial dysfunction and cardiomyocyte injury. Transtuzumab processing has led to an increase in PTX3 levels depending on the time and dose and led to a decrease in intracellular calcium levels, which leads to a violation of a reduction in cardiomyocytes. Inhibition of PTX3 increased intracellular calcium levels and improved contractile dysfunction of cardiomyocytes. Other studies show that HER2 inhibition by trasutsumab activates EGFR and activated EGFR contributing to the increase in PTX3 and increased secretion, while dual EGFR / HER2's lapinib inhibitor decreases the level of PTX3. It indicates that it will be done. Other studies show that the trusutsumab has increased the Stat3

phosphorylide stat3 level, and lapachinib has reversed this result. Trastuzumab was shown to activate EGFR/STAT3 signaling in vascular endothelial cells, promoting the release of PTX3 and inhibiting cellular calcium signaling, ultimately leading to reduced contractility in cardiomyocytes. Meanwhile, lapatinib was identified as a viable drug to prevent trastuzumab-induced cardiac complications.

Doxorubicin is widely used clinically to treat breast cancer, but resistance develops in a short period of time. Breast cancer drug resistance features are mainly associated with the P-glycoprotein (P-gp) encoded by the ABCB1 gene, which uses the energy generated by ATP hydrolysis to pump chemotherapeutic drugs out of the cell, thus reducing the concentration of effective intracellular drugs and mediating chemotherapy resistance, and whose expression and function are mainly regulated by signalling pathways, such as PI3K/AKT/mTOR, MAPK, NF-κB, and so on. Both breviscapine and ivermectin can alleviate doxorubicin resistance by inhibiting EGFR, probably due to their competitive binding to the P-gp substrate binding site, reducing P-gp-mediated doxorubicin efflux and enhancing the efficacy of chemotherapy. (Design 2024)

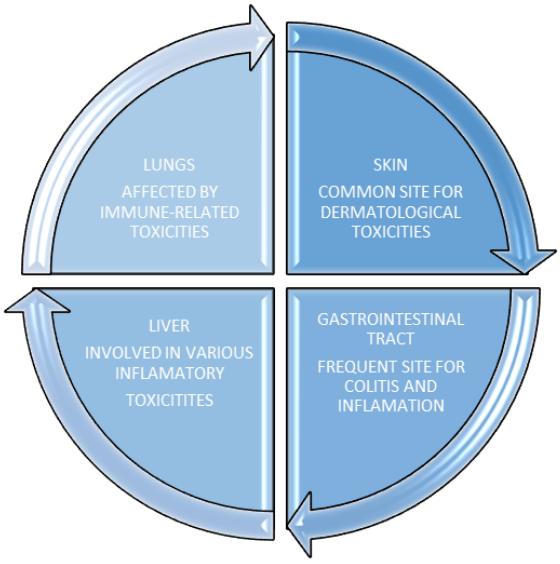
IMMUNE CHECKPOINT INHIBITORS:
Why do certain organs experience immune-related adverse events (irAEs) more frequently than others?

This results in a variety of inflammatory toxicities that could potentially affect nearly any organ in the body. However, many of these toxicities are often restricted to specific 'barrier organs' such as the skin, gastrointestinal tract, liver, and lungs . While most of these adverse effects are mild, serious toxicities from any of these organs can pose significant risks to life.Among the most serious toxicities attributed to current immune checkpoint inhibitors (ICIs) is colitis. Approximately 20% of patients undergoing PD-1 blockade experience some form of mild gastrointestinal inflammation, while 2–5% develop more severe inflammation. With CTLA-4 inhibitors, gastrointestinal inflammation arises in about 40% of patients, with 10–15% experiencing severe cases.

Dermatological toxicities are even more prevalent, impacting the majority of patients receiving ICI treatment. Although most of these adverse effects are mild and can often be managed with topical treatments, severe reactions can also occur. The frequent involvement of barrier organs indicates that the immune response may be targeting the commensal microbiome, although this has yet to be proven. The adaptive immune system develops through a selection process that removes most high-affinity self-reacting T and B cells Conversely, immune cells that respond to harmless microbial and environmental proteins are regulated solely by peripheral tolerance mechanisms such as the CTLA-4 and PD-1/PD-L1 pathways. In fact, inflammation in barrier organs is characteristic of numerous genetic disorders related to peripheral tolerance mechanisms, including CTLA-4 heterozygosity.(Wang, Dougan, and Dougan 2023)

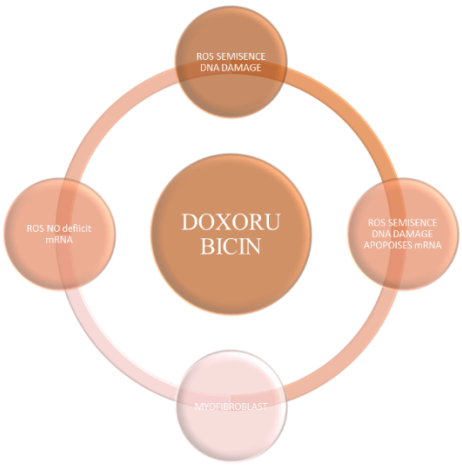
ICI ability to detect and destroy cancer cells. However, their use can lead to side effects of the immune system with immune-mediated adverse events because of the immune system dysregulation. Since their approval in 2014, these etc. adverse Myocarditis events has have recently been been noted reported in as the a neurological, side endocrine, effect pulmonary, of gastrointestinal ICI and therapy renal in systems, small case series, but clinical presentation, risk factors and years outcomes ago, are almost still 600,000 not people well in established.

Not the quite United 4 States may have been eligible for ICI therapy, and its use is predicted to rise dramatically in the coming years. This underlines the importance of understanding myocarditis with ICI. After a few isolated cases were reported, researchers set up a retrospective and prospective multicenter registry in response. This registry of 35 patients with myocarditis following ICI treatment compared them time. with Cardiovascular other outcomes, patients along not with having clinical myocarditis presentation, who treatment, were and treated diagnostic with testing ICI for around these the outcomes same were examined.(Chen etal.2018) among the various formats Of ICI-related cardiotoxicity (ICI), cardiomyopathy is the most recognized cause of significant morbidity and mortality. But there are also other heart symptoms such as heart muscle abnormalities. Arrhythmia acute coronary syndrome and inflammation of the blood vessels as well the exact mechanism behind its cardiotoxic effects is not fully understood. But the existence of similar T-cell receptor sequences in tumors and cardiomyocytes. It shows the feasibility of using a combination of antigen targets. Animal studies show that CTLA-4, PD-1, PD-L1, and immune damage under stress provide cardioprotective effects. This means that inhibition by ICI may make heart cells more vulnerable to damage... A global multicenter registry reports the overall prevalence of ICI-associated myocarditis to be 1.14%, with the rate of patients receiving combination therapy (using two or more ICIs) increasing to 2.4%. Troponin levels increased in 10% of nivolumab-treated patients without apparent cause, indicating sub-optimal or mild treatment. The true incidence of myocardial infarction may be higher. The true incidence of Myocardial infarction from ICI remains unclear and may be underestimated due to a number of factors. including the absence of specific clinical symptoms Potential for overlap with other cardiovascular conditions Diagnostic challenges and limited awareness of this problem. Risk factors for ICI-related cardiotoxicity remain poorly understood, however, international registries list factors such as combination therapy, diabetes, obesity, and anti-CTLA-4 therapy as risk factors. that is independent Pre-existing autoimmune diseases can also increase your risk. There is also a trend.(Li *et a* 2023)



As cancer grows and spreads bad cells build up genetic changes that make them produce various neoantigens. At first, the body's defense systems try to stop tumor growth. But cancer cells can dodge these defenses—a process called immunosurveillance—either by (Varricchi et al. 2017)picking tumor cells that trigger less of an immune response (immunoediting) or by shutting down immune responses. Even though immunologists and cancer doctors have put a lot of work into turning on anti-tumor immune responses early tries didn't work well for 10](Varricchi *et al*. 2017)several reasons. Pathways that slow things down like CTLA-4 PD-1, and PD-L1 cut down the ability of T cells to attack tumors. These pathways play a key role in keeping the body from attacking itself and stopping autoimmune diseases. Tumors use them to avoid T cell attacks. The game-changing work by Allison and his team showed that tumors use checkpoint inhibitor activation as one of the main ways they hide from the immune system. In recent years, treatments targeting these immune checkpoints with antibodies such as anti-CTLA-4 anti-PD-1, and anti-PD-L1, have caused a sea change in cancer immunotherapy for many types of cancers.(Varricchi et al. 2017)

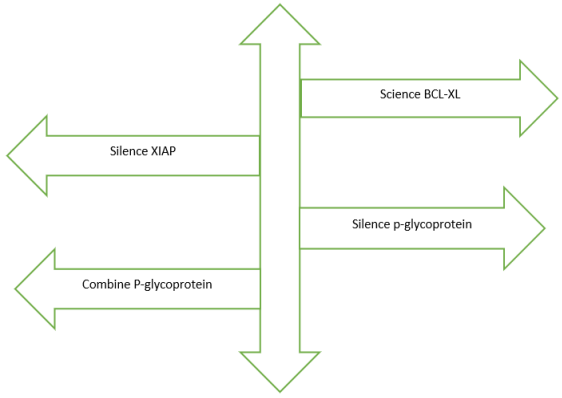
Immune chack point inhibitors such as PD-1/PD-L1 and CT:A-4 inhibitors,have revolutionarily cancer therapy by enhancing the immune system ability to attack tumaors.however,these agents are associated with immune related adverse events (irAEs) including carditoxicity,which can be serve and life-threating



Immune-related adverse events (irAEs) are more common in patients receiving ICI therapy, such as anti-CTLA-4 and anti-PD-1/PD-L1 therapy. There was an incidence of 5 irAEs, classification according to dose. Studies show that anti-CTLA was reported in 90% of patients treated with -4 and anti-PD-1 in 70% of patients treated with anti-PD-1. /PD-L1 has some experience with grade 3/4 forms Toxicity Low toxicity, with 21% in 50 trials. IrAE is organ specific. Skin reactions (burning, itching, etc.) are the most common. This is followed by gastrointestinal problems (e.g. diarrhea, colitis) and endocrine disorders (e.g. thyroid disorders). Other toxicities include musculoskeletal pain. Eye problems... Pneumonia, myocarditis neurotoxicity And nephritis is rare but has serious side effects. The severity of irAE can lead to high mortality. This is especially true of myocardial infarction (39.7% of deaths) and neurotoxicity (such as encephalitis) and muscle weakness. muscle weakness type) Combination therapy, such as using anti-CTLA-4 with anti-PD-1/PD-L1 inhibitors, causes side effects more often than monotherapy. Different drugs that target the same immune checkpoint can cause different toxicities. Some agents, such as nivolumab, are associated with higher rates of endocrine disorders. Pembrolizumab This causes more arthritis, pneumonia, and liver problems. The same is true for treatment with anti-PD-L1 drugs such as atezolizumab. hypothyroidism Nausea and vomiting may occur. There are also different tumor patterns, such as an increase in vitiligo in melanoma patients. Compared to other cancer patients (Yin *et al.* 2023)

Get pasha by induction of apoptosis mechanisms by doxorubicin in chondrosarcoma cells. One schematic illustrates the molecular cascade of apoptosis induced by doxorubicin. As stated, doxorubicin causes DNA damage. The DNA damage leads to the release of cytochrome C from the mitochondria, and activation of caspases, the agents of apoptosis. The same protein causing resistance to doxorubicin release is p-glycoprotein. Bcl-2 genes and Bcl-xL genes prevent cytochrome c release, while XIAP prevents caspase activation. We analyzed the impact of silencing antiapoptotic genes. Silencing Bcl-xL and XIAP increased doxorubicin sensitivity to similar levels compared to those targeting P-glycoprotein, whereas combined silencing of Bcl-xL with P-glycoprotein and XIAP with P-glycoprotein was significantly more effective in our dual gene silencing group. It seems

probable that a P-glycoprotein-overexpressed tumor cell line exhibiting Bcl-xL and XIAP expression could imply a high level in relation to a lesser prognosis regarding treatment resistance . On the other hand, apoptosis leads to proteolytic activation of P-glycoprotein, which may, in essence, result in enhanced sensitivity toward apoptosis.On the other hand, transient transfection barely affected the induction of apoptosis for the SW1353 chondrosarcoma cells. However, Bcl-2-specific inhibitor treatment improved the cell sensitivity to doxorubicin within SW1353 cells compared with the negative control group There might be low knockdown efficiency of Bcl-2 Bcl-2 inhibitors equally interact with Bcl-xL and Bcl-2 as they both compete for binding with the Bak BH3 peptide in both Bcl-xL and Bcl-2(Kim *et al*. 2009)



VEGF Inhibitors and multi Targeted Kinase Inhibitors:

Inhibition of angiogenesis is a mainstay of treatment for many cancers. The vascular endothelial growth factor (VEGF) pathway is the primary target. Bevacizumab, a monoclonal antibody that blocks VEGF, is the first such therapy to be developed. It is used in combination with chemotherapeutic agents to treat a variety of solid tumors. Renal cell cancer including colon cancer, ovarian cancer, uterine cancer, glioblastoma… Other strategies to inhibit angiogenesis These include soluble VEGF receptor decoys, VEGF receptor (VEGFR) antibodies, small molecule tyrosine kinase inhibitors (TKIs).) and unlike monoclonal antibodies, which bind VEGF with high specificity, TKIs have a Broad spectrum action in non-angiogenic sms involving several tyrosine kinase receptors, such as platelets from growth factor receptor targeting fibroblast growth factor receptor c-KIT etc. This broad action is usually toxic non-targeted It causes. Considering the important role of VEGF in maintaining vascular homeostasis, cardiotoxicity is therefore a common side effect of these therapies. The cardiovascular side effects of bevacizumab are well documented in clinical trials and broad-spectrum studies, but the extent of cardiovascular side effects from targeted anti-VEGF TKIs is unknown many results are unclear Hypertension, thromboembolic events by meta-analysis of trials involving sunitinib, sorafenib, and pazopanib (ATEs), a reduction in the risk of left ventricular ejection fraction (LVEF) was observed compared with the control group. Interestingly, VEGF TKIs were associated with increased vascular injury. No events (VTE) were reported, possibly due to underreporting. Because only cancer can increase the risk of VTE, whereas these studies may underestimate the true extent (Vallerio *et al.* 2022).

TKIs and Anti BCR-ABL Agents

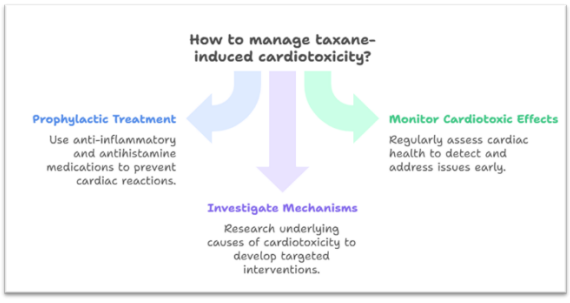
The treatment for the patients suffering from chronic myeloid leukemia has completely changed due to the arrival of tyrosine kinase inhibitors targeted therapy. However, the cardiotoxicity associated with the drugs. These therapies also place survivors of cancer at higher risk. For the T315I mutated gatekeeper that renders the patient resistant to imatinib, nilotinib, dasatinib, and bosutinib, there exists a third generation TKI named ponatinib. The most cardiotoxic FDA-approved TKI within the entire family of FDA-approved TKIs (more than , as assessed in multiple objective screenings performed by our lab and other labs, is ponatinib. Actually, the only drug available for the treatment of CML patients harbouring a T315I mutation is ponatinib. The cardiovascular risks and mechanisms associated with CML TKIs are the leading focus of this review, especially as related to ponatinib cardiotoxicity.

Inhibition of angiogenesis is an informative strategy on which most most cancers remedies are based totally, with the vascular endothelial growth thing pathway being one of the principal goals The first step is to goal VEGF so it's far a monoclonal antibody, which used to deal with several styles of solid tumors : colorectal carcinoma, renal mobile carcinoma; In addition to bevacizumab, other angiogenesis inhibitor

therapies were identified for cervical most cancers, ovarian cancer, and glioblastoma. These include soluble VEGF decoy receptors, anti-VEGF receptor (VEGFR) antibodies, and small molecule tyrosine kinase inhibitors (TKIs). Unlike monoclonal antibodies, which might be regarded to bind VEGF with excessive affinity specificity, TKIs act in a very nonspecific way. A 2nd mechanism by means of which TKIs further goal non-anginogenic goals is regularly discovered in the ATP-binding pockets of tyrosine kinase receptors even though greater useful, this results in non-toxicity the target comes into them Because VEGF plays such an crucial function in vascular health, cardiotoxicity is one of these such chemical aspect results . While the cardiovascular dangers of bevacizumab are widely recognized from randomized medical trials and extended studies, this is not the case for sunitinib, sorafenib, and pazopanib anti-VEGF TKIs Blood strain and LVEF are the threat of increases in correlation or uncertainty (Soiza, Donaldson, and Myint 2018)

Taxanes:

Taxanes: Taxanes, along side paclitaxel, are antimitotic sellers that stabilize microtubules within the mitotic spindle, therefore blocking cell cycle development. These chemotherapy capsules are extensively hired in most cancers remedy, which includes breast, lung, and ovarian cancers. However, sizable toxicities limit the effectiveness of taxanebased remedy regimens (eighty). Taxane management is recommended to bring about cardiotoxic events in 3–20% of the sufferers (80 one, 82). Taxane-triggered cardiotoxic consequences consist of QT c program language period.



prolongation, found through the usage of bradycardia and atrial fibrillation (eighty two). The underlying mobile and molecular mechanisms of taxane-brought on cardiotoxicity are uncertain; however, a few hypotheses were proposed. Among them, allergy response with a huge histamine launch and consequent disturbance of the conduction tool and arrhythmia has been proposed (80). Hence, the management of anti inflammatory (glucocorticoids) and anti- histamine pills (histamine receptor blockers), is normally encouraged as prophylactic treatment for the manage of cardiac anaphylaxis brought approximately by taxanes [reviewed in . Another speculation is cardiomyocyte harm via the drug's moves on subcellular organelles (eighty two). In this regard, taxanes had been encouraged to growth ROS manufacturing with the aid of the use of cardiomyocyte mitochondria, the hole of mitochondrial permeability transition pore and the crumble of mitochondrial membrane ability(Morelli et al. 2022)

Flurouracil ECG modifications with57,fifty eight or without immediately observedcoronary vasospasm on preliminary challenge with five-FU,similarly suggesting a position for easy muscle featurein five-FU-related coronary vasospasm.Nevertheless, there have been a few inconsistencieswith the concept of vasospasm and 5-FU administration. Coronary vasospasm has now not been continuouslyproven at angiography in the course of symptomaticepisodes, even after reintroducing 5-FU in topicsknown to have had previous cardiac symptoms following five-FU management. Amongst patientssuspected of getting five-FU-related cardiotoxicity,vasospasm turned into no longer proven on pharmacologicprovocation with the alkaloid ergonovine,seventy four an agentthat has formerly been used to assess coronaryvasomotor function via its movement on cleanmuscle serotonergic receptors, which in flip leadsto muscle contraction and vasoconstriction underphysiologic situations.Seventy five Furthermore, in a single take a look atof patients who said angina in response to afive-FU assignment who had ECG modifications suggestiveof ischemia, folks that underwent concurrent echocardiography were proven to have global akinesia,incompatible with a feature territorial distribution of a first-rate coronary artery.5 Despite the systemic distribution of five-FU, multivessel coronaryvasospasm is unusual in patients receiving5-FU.Seventy six,77 Indeed, when assessing sufferers with strong angina de novo at coronary angiography,

epicardial vasospasm is likewise typically discovered in a singlevessel,sixty three,sixty six which is regularly the vessel supplying thelargest territory of myocardium. This can be associatedto an oxygen supply–call for mismatch, however thisexplanation has not been completely elucidated yet. Thediscordance among echocardiographic and angiographic findings may want to undermine the epicardialvessel vasospasm (Soiza, Donaldson, and Myint 2018).

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