Developments of new medications are one of the vital components of advanced medical care. As clinicians, we need to be vigilant on dealing with these medications, some used in the management of patients in oncology, hematology, rheumatology, dermatology and gastroenterology. Many are now potentially affecting our cardiac patients. Following is not a classified description of cardiotoxic medications, but rather just an insight to diverse groups of medications that are exceedingly used and their challenging cardiovascular side effects in terms of diagnosis or management.

Until recently, interaction between cardiology and oncology was mainly focused on Anthracycline induced myocardial dysfunction [1] or radiation induced pericardial/ myocardial damage [2]; however, due to increased age and survival of cancer patients, the incidence of cardiotoxicity has also increased [3]. Patients suffering from medication related cardiovascular toxicity can be included in different categories:

1) Patients with pre-existing cardiac diseases,
2) Those with just cardiovascular risk factors
3) patients who previously received chemo therapy and, later developed cardiovascular conditions and
4) who had no prior cardiac disease but just developed cardiac side effects.

Recently, cardio-oncology clinics are developed to address concern on oncology related cardiotoxicity; however, it appears that current era of therapeutics affecting heart or vascular system is not limited to cancer medications but use of such medications are now extended to multiple specialties, covering large patient population.

These medications could potentially affect the heart by different mechanisms. First, some drugs directly target cardiac cells or pericardium causing myocardial systolic dysfunction or pericarditis. Second, is the risk of arrhythmia such as atrial fibrillation (AF). Third, some drugs can increase thromboembolic events causing cardiovascular or cerebrovascular events. Fourth, hypertension commonly associated with anticancer agents, causing early or delayed effects on cardiovascular system.

Biological products are wide range of products such as vaccines, blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They may be composed of proteins, sugars, nucleic acids or living cells and tissues. They are often used to treat a variety of medical conditions for which no other treatment is as effective, such as inflammatory arthritis, colitis, cancer, and neurological conditions. They include monoclonal antibodies (mAb), tumor necrosis factor inhibitors (TNF), IL-6 antagonist (Tocilizumab), anti-CD28 (Abatacept), interleukin (IL)-1 antagonist (Anakinra), and anti-B cell (rituximab). There are numerous adverse effects of these medications that are related to their specific targets, including infections and cancer, autoimmune disease but my emphasis is on their organ-specific adverse events, most specifically cardiotoxicity.

Angiogenesis, a normal process in which new blood vessels are created and our vascular system regenerates, it is a vital process in wound healing, growth, and development. However, growing tumors hijack this process to feed and proliferate tumor cells [4], making angiogenesis a key factor for tumor growth. Targeting angiogenesis has shown to halt cancer growth but predictably affects cardiovascular system.

There are some modalities to inhibit cancer related angiogenesis such altering vascular endothelial growth factor (VEGF) signalling cascade. VEGF plays a critical role in angiogenesis. Another popular target for cancer therapies is the human epidermal growth factor receptor 2 (HER2). The HER2 protein is overex-
pressed in 15–30% of patients with breast cancer. Current antiangiogenesis therapies, including the inhibition of VEGF, have shown to have adverse effects on the cardiovascular system [4].

Trastuzumab (Herceptin; Genentech), a humanized mAb directed against human ERBB2 was fast-tracked by the FDA to gain approval in September 1998. Perhaps when it was successfully used in women with metastatic breast cancer, there was no significant insight to its cardiotoxicity but further experiments in laboratory animals indicated that some monoclonal antibodies, including trastuzumab, when bound to a cell causes cell injury by antibody-dependent cell-mediated cytototoxicity. Trastuzumab is associated with cardiac dysfunction [5], which includes congestive heart failure. Its cardiotoxicity is an on-target effect due to blocking downstream signalling from HER2, and causing MOMP, cytochrome-c release and caspase activation, resulting in apoptosis of cardiac muscle cells with impaired contractility and reduced ventricular function, it also downregulates neuregulin-1 (NRG-1), which is essential for the activation of cell survival pathways in some cells such as cardiomyocytes, affecting cardiac function.

Myocardial dysfunction is not the only cardiac related side effect of the above mentioned medications. Drug-induced immune thrombocytopenia, increased thrombogenicity, blood pressure fluctuations, arrhythmia and increased likelihood of cardiovascular events including acute myocardial infarction can also be caused by these new products. As for example, acute thrombocytopenia may be caused by infliximab. This medication blocks the effects of tumor necrosis factor alpha, a substance made by cells of the body which has an important role in promoting inflammation. This monoclonal antibody is currently used on many inflammatory diseases such as Crohn’s disease, rheumatoid arthritis, psoriasis /psoriatic arthritis and ankylosing spondylitis.

We also need to elaborate other groups of medications emerged into the management of patients mainly in the field of oncology and haematology. Tyrosine kinases inhibitors block downstream signalling pathways and inhibit downstream expression of vascular endothelial growth have been proven to be effective anti-tumor agents and anti-leukemic agents, they too are considered to be affecting cardiovascular system. Imatinib used for chronic myelogenous leukemia (CML), Philadelphia chromosome-positive acute lymphocytic leukemia (ALL) and resistant gastrointestinal stromal tumor (GIST). Latter another multi-targeted receptor tyrosine kinase inhibitor, Sunitinib was discovered. It was effective in the treatment of renal cell carcinoma (RCC); Sunitinib is associated with onset of severe hypertension.

Some vascular endothelial growth factor ligand inhibiting agents demonstrate specific toxicities that differ from common chemotherapy medications. Bevacizumab, VEGF-targeting agents medication sold under the trade name Avastin, is commonly used for management of colon cancer, lung cancer, glioblastoma, and renal-cell carcinoma. Besides cancer, it is also used for the management of age-related macular degeneration, through injection into the eye [6] and has been associated with increased risk of vascular thrombosis.

More recently introduced Anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed cell death protein-1 (PD-1) which enhance the cytotoxic immune response to the cancer cells [9] and Adoptive T cell transfer (ACT) as well as chimeric antigen receptor (CAR)-T therapy new promising methods using patient’s T cells to specifically target tumor cells. However, the therapeutic effects may be counterbalanced with cardiotoxic effects. Cardiomyopathy, myocardial fibrosis, myocarditis, and acute heart failure, were also reported in single anti-CTLA-4 or anti-PD-1 treatment [7].

To further add to this challenge, currently there is no consensus definition of cardiotoxicity and difficulties exist in detecting cardiotoxic damage caused by these medications. Use of imaging modalities such as echocardiography, MUGA or cardiac MRI as well as biomarkers, such as BNP and troponin are useful but neither are the ultimate diagnostic modalities.

One of the traditional foci of cardiac imaging have been monitoring the baseline and post-treatment of left ventricular ejection fraction mostly through the use of echocardiography or multiple gated acquisition nuclear scans [8] and more recently, Cardiac magnetic resonance (CMR) imaging, by virtue of its accurate depiction of cardiac morphology and function but still we are far from reaching practical gold standards for the assessment and management of cardiototoxicity caused by these therapeutic modalities.

In summary physicians should be vigilant on dealing with above mentioned new medications. The exact intersection of cardiology and targeted immune therapy is not well clear and diagnostic options are still limited. Awareness on potential cardiotoxicity related to each medication, pre and post medication surveillance, use of proper imaging modality and screening high risk patients for the development of cardiotoxicity are some keys to safer management.

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