CARDIOTOXICITY OF ANTICANCER DRUGS

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Cardiotoxicity of Anticancer Treatment

Advances in the treatment of cancer aim to increase the survival of patients suffering from this disease. Since more patients survive and reach an older age, long-term complications of their anticancer treatment, such as cardiotoxicity, may surface increasingly. In addition to chest wall irradiation, several cytostatic agents,[1] of which the anthracyclines are the most important, can induce cardiotoxicity. These cardiovascular complications can occur acute (during administration), early (several days to months following administration), or late (years to decades following exposure). Therefore, prediction and early detection of cardiotoxicity, preferentially before symptoms of cardiac dysfunction develop, are becoming increasingly important in the follow-up of cancer patients. Primary prevention and early intervention are of imminent importance.

Anthracyclines: Anthracyclines group includes Adriamycin (Doxorubicin), Daunorubicin, Epirubicin, Idarubicin and Mitoxantrone are particularly well known for their cardiotoxicity. The mechanism of cardiotoxicity involves the formation of a stable complex of drug with ferric iron, which reacts with oxygen, forming superoxide anions, hydrogen peroxide, and hydroxyl radicals. These free radicals cause lipid peroxidation.[2] The incidence of early cardiotoxicity particularly increases when the cumulative dose exceeds a certain threshold. For Adriamycin this is 450[3] mg/m^2, for epirubicin 900-1000 mg/m^2, for daunorubicin 550 mg/m^2, and 160 mg/m^2 for mitoxantrone.[4] In fact, data from prospectively evaluated patients show the probability of developing Congestive Heart Failure (CHF) at 400 mg/m^2 to be 4.9%, at 450 mg/m^2 to be 7.7%, and at 500 mg/m^2 to be 20.5%.[5] According to American Society of Clinician Oncology ASCO guideline[6] published in 2001, incidence of clinical CHF is greater than 5% at the cumulative dose of 450 mg/m^2 of Adriamycin on 6 month follow up after the last cycle. Acute cardiotoxicity is uncommon, but can consist of arrhythmias, left ventricular dysfunction, a peri-myocarditis syndrome or electrocardiographic abnormalities. Late cardiotoxicity can occur up to years after treatment and consists of CHF due to non-ischemic dilated cardiomyopathy, which is considered to be irreversible.[7]

Cyclophosphamide: Cyclophosphamide for instance, can lead to cardiac dysfunction. However, the incidence is low and this is almost exclusively encountered with administration of high doses, such as used before bone marrow or stem cell transplantation.[8]

Fluorouracil: Fluorouracil is another agent that is associated with cardiotoxicity, with symptoms varying from cardiac arrhythmias, silent myocardial ischemia, angina, congestive heart failure and even sudden death.[9]

Paclitaxel: Transient Bradycardia and heart block have been observed with Paclitaxel, but the clinical significance of these cardiotoxic events is unclear. However, paclitaxel used in combination with Adriamycin was found to increase the risk of Adriamycin-induced heart failure, as was observed in 18% of the women treated with this combination for metastatic breast cancer.[10]

Transtuzamab (Herceptin): The use of Transtuzamab either as a single agent, or in combination with chemotherapy can improve survival of patients with metastatic disease of HER2-positive breast cancer. A retrospective analysis of a phase III study however, revealed an increased incidence of heart failure, especially among patients treated with the combination

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of Adriamycin-cyclophosphamide and trastuzumab (27%); in the patients treated with paclitaxel and trastuzumab, heart failure occurred in 13%. Single agent trastuzumab resulted in only 4% cardiotoxicity which is thought to be reversible.[11]

Detection of Chemotherapeutic Agent Induced Cardiotoxicity

The standard clinical approach for monitoring cardiotoxicity induced by antitumor agents includes assessment of baseline cardiac performance before therapy begins, regular monitoring during treatment and long term follow-up after therapy has been completed. Various diagnostic procedures are listed in Table 1.[7]

Diagnostic Procedures	Characteristics
Physical examination and clinical history	Lack of Specificity
Electrocardiography: arrhythmias, flattening of T wave, prolongation of QT interval, decrease in R-wave voltage	Lack of Specificity
Serial ECHO and radionuclide MUGA imaging: decrease in left ventricular ejection fraction	Highly reliable, wide use and availability
Endomyocardial biopsy	Greatest reliability Relatively high expense Availability in only a few centers

Table1: Procedures for the diagnosis of anti-cancer drug induced cardiotoxicity

The "gold standard" for monitoring cardiotoxicity of anticancer is the direct microscopic visualisation of the cardiac tissue, i.e. endomyocardial biopsy; however, this method is not performed in clinical practice, because of technical complexity and limited availability.[12]

A change in the LVEF, as determined by echocardiogram (ECHO) or multi gated acquisition (MUGA) scan, is a very good indicator of developing cardiomyopathy; monitoring for such a change should be frequent during treatment and regular thereafter, throughout the patient's lifetime.[13] It has been well documented that serial ECHO or MUGA can detect declines in LVEF and predict risk of clinical as well as subclinical cardiomyopathy and CHF after cumulative exposure to anticancer agents.[6]

Echocardiography: Serial echocardiographic measurement of the LVEF is a sensitive noninvasive tool for the primary detection and follow-up of anticancer induced cardiomyopathy, as well as an easy and relatively low-cost procedure.[14] One advantage of ECHO over radionuclide MUGA is that it does not expose patients to ionizing radiation. But the quality of examination depends upon the skill of operator, with assessment of LVEF by different operators in the same patient varying by 15% (inter-observer variability).The result of the inadequate assessment is that the reproducibility of the technique is poor, with an inter-observer variability of 11% for ejection fraction. This worsens in badly impaired ventricles.[15]

Multigated Acquisition (MUGA): MUGA scanning is highly reproducible and probably more sensitive than ECHO at detecting early changes in LVEF.[12] The mean inter- and intra-observer variability of assessing the ejection fraction studied <2%,[16] and the inter-study variability reported <5%[16] at rest and <2% with exercise.[17] Several early studies demonstrated an excellent correlation of MUGA-derived LVEF with values obtained by cardiac catheterization contrast ventriculography.[18] In a pooled analysis of three trials with serial monitoring of left ventricular function, more than one third of patients who went on to develop CHF secondary to Adriamycin demonstrated a > 30% reduction in LVEF before the onset of symptoms.[19]

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function.[20]

Role of Cardioprotective Agents

Anthracyclines is associated with a decrease of the endogenous antioxidant enzymes, such as glutathione peroxidase, that are responsible for the scavenging of free radicals. The American Society of Clinical Oncology

(ASCO) sought to establish evidence based clinical practice guidelines for the use of dexrazoxane. It is not routinely recommended for patients with metastatic breast cancer who receive initial Adriamycin based chemotherapy or who have received a cumulative dosage of 300 mg/m^2 or greater. The use of dexrazoxane in the adjuvant setting is not recommended outside of a clinical trial.[1]

In addition to early detection, prevention or circumvention of cardiotoxicity by antineoplastic treatment is also of interest. Attempts to improve cardiac safety of potentially cardiotoxic anticancer agents include alterations of dosing schedules to modify pharmacokinetics, for instance altered dosing schedules. Administration of liposome-encapsulated anthracyclines represent the most recent approach to the problem of anthracyclines induced cardiotoxicity, without attenuating antitumor efficacy. Clinicians are trying to find methods to identify patients who will develop cardiotoxicity of anticancer treatment, in order to be able to intervene earlier and prevent or limit clinical symptoms.

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