THE WAY FORWARD: AN EMERGING FIELD OF CARDIO-ONCOLOGY

MARIANNA KRIVE, DO
ADVOCATE HEART INSTITUTE
AMGEN-PARKSIDE CARDIOLOGY

LEARNING OBJECTIVES

1. Explain the foundation and the medical need for cardio-oncology program within cancer center.
2. Describe cardiology challenges facing cancer patients and survivors.
3. Identify strategies to minimize long term cardiac toxicities and events for oncology patients.

CARDIO-ONCOLOGY

• New comprehensive discipline
• Identifies & prevents cardiac toxicities of cancer treatment
• Aims to improve the overall acute and long-term outcomes of cancer patients
• Develops interdisciplinary expertise to manage the growing category of cancer survivors.

Cardiology and Oncology. Why to Discuss Together......

• The two most common disease conditions in the developed world
• Cardiac disease may pre-exist cancer therapy or may be caused by it
• Cancer therapy is more effective than ever before
• 14 million cancer survivors in the United States now and 19 million cancer survivors in the United States by 2024
• Oncologists & cardiologists have the best HEART.

Mortality in the US - 1950-2014: Heart or Cancer......

New Therapies: Newer Toxicities....RCC

CDC.GOV

Cardio-Oncology History in the North America

1990 Cardiologists focus on cancer
2005-2006 Cardio-Oncology partnership
2011 Canadian Cardio-Oncology Network
2017 ACC Cardio-Oncology Conference

Reasons for Collaboration

Cardio
- Pre-therapy: Cardiac Risk Assessment
- During therapy: Prevention of Cardiomyopathy
- Post-therapy: Monitoring for Cardiac Complication

Oncology
- Pre-therapy: Evaluation of Patients with Known Heart Disease
- During therapy: Early Diagnosis of Oncology Patients with Existing CV Disease
- Post-therapy: Long Term Risk Assessment

Learning Objectives

1. Explain the foundation and the medical need for cardio-oncology program within cancer center.
2. Describe cardiology challenges facing cancer patients and survivors.
3. Identify strategies to minimize long term cardiac toxicities and events for oncology patients.

Cardio-Vascular Complications of Chemotherapy and Radiation

1. Myocardial dysfunction and Heart failure
2. CAD
3. Valvular disease
4. Arrhythmias, often induced by QT prolonging drugs
5. HTN
6. Thromboembolic disease
7. Pulmonary hypertension
8. PVD and stroke
9. Pericardial complications

Heart Failure – Definition of Cardiotoxicity

- Definition: Decline in LVEF >10%
- Modest: Decline in LVEF >10% to Final LVEF <45%
- Severe: CHF

- Evaluation:
  1. Decrease in LVEF globally or more severe in the septum
  2. Signs and symptoms of HF
  3. Decline of EF ≥5% to final LVEF <55% with symptoms of CHF
  4. Asymptomatic decline of LVEF ≥10% to final LVEF <55%

- Imaging:
  1. Decreased ejection fraction on 2D ECHO
  2. Decreased wall motion on 2D ECHO
  3. Decreased LV mass on CMRI
  4. Decreased global longitudinal strain on MRI
  5. Increased mitral valve annular dilatation on CMRI

- Cardio-review and Evaluation:
  1. Decrease in LVEF ≥10% to final LVEF <55%
  2. Signs and symptoms of HF
  3. Decline of EF ≥5% to final LVEF <55% with symptoms of CHF
  4. Asymptomatic decline of LVEF ≥10% to final LVEF <55%

- Treatment:
  1. Antioxidants
  2. Statins
  3. Angiotensin-converting enzyme (ACE) inhibitors
  4. Beta blockers
  5. Future therapies
Risk for Developing Heart Failure?

- High dose anthracycline (e.g. >250 mg/m^2 doxorubicin, >600 mg/m^2 epirubicin)
- Lower dose anthracycline (<250 mg/m^2 doxorubicin, <600 mg/m^2 epirubicin) in combination with lower dose radiotherapy (<30 Gy) where the heart is in the treatment field

**NEW CV GUIDELINE IN ONCOLOGY WORLD**

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancer: American Society of Clinical Oncology Clinical Practice Guideline

- Multiple cardiovascular risk factors: smoking, hypertension, diabetes, dyslipidemia, obesity during or after completion of therapy.
- Older (≥60 years) age at cancer treatment.
- Compromised cardiac function (borderline low LVEF, history of MI, emoderate to severe valvular heart disease) at any time prior to or during treatment.

**Risk for Developing Heart Failure**

Treatment with lower dose anthracycline (<250 mg/m^2 doxorubicin, <600 mg/m^2 epirubicin) or trastuzumab alone, and presence of any of the following risk factors:

- Multiple (≥2) cardiovascular risk factors: smoking, hypertension, diabetes, dyslipidemia, obesity during or after completion of therapy.
- Older (≥60 years) age at cancer treatment.
- Compromised cardiac function (borderline low LVEF, history of MI, emoderate to severe valvular heart disease) at any time prior to or during treatment.

**CAD and ACUTE CORONARY SYNDROME**

- STEMI has a higher mortality rate in cancer patients.
- Malignancy diagnosed within 6 months of PCI have a 3-fold higher mortality rate than those diagnosed with a malignancy >6 months after PCI.
- Induced by chemotherapy, radiotherapy, or the combination.
TAKOTSUBO CARDIOMYOPATHY

- Prevalence 10-20%.
- Detrimental event in the overall prognosis of the patient with cancer.
- Less benign than previously considered.
- Median survival in patients with Takotsubo and cancer was 30 months (vs 60 months in patients with cancer and NSTE MI).

MECHANISMS OF CAD IN CANCER TREATMENT

<table>
<thead>
<tr>
<th>AGENT</th>
<th>PATHOPHYSIOLOGY</th>
<th>RISK OF CAD AND ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoropyrimidines 5-FU, capecitabine, gemcitabine</td>
<td>Ischemia</td>
<td>Up to 18% manifest myocardial ischemia</td>
</tr>
<tr>
<td>Platinum compounds Cisplatin</td>
<td>Procoagulant status Arterial thrombosis</td>
<td>20-year absolute risk up to 8% after testicular cancer</td>
</tr>
<tr>
<td>VEGF inhibitors Bevacizumab, Sorafenib, Sutinib</td>
<td>Procoagulant status Arterial thrombosis Endothelial injury</td>
<td>Risk of arterial thrombosis Bevacizumab 3.8% Sorafenib 1.7%, Sutinib 1.4%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Endothelial injury Plaque rupture Thrombosis</td>
<td>2-7% increased risk of MI Cumulative 30-year coronary events incidence of 10% in Hodgkin’s lymphoma survivors</td>
</tr>
</tbody>
</table>

RADIOThERAPY-RELATED CVD

- Nested case-control study of 325 Hodgkin survivors (26-50 y.o. from 1965-1995) compared to 1204 controls.
- CHD (MI or angina requiring intervention).

QT PROLONGLATION

What is normal?
- < 450 ms in men
- < 460 ms in women

What is concerning?
- QTc > 500ms
- Increase in QT > 60 ms

Drug agents associated with QT prolongation and Torsades de Pointes

<table>
<thead>
<tr>
<th>Drug agent</th>
<th>QTc (ms)</th>
<th>Effect size</th>
<th>Group (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Sutinib</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Carmustine</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

What is normal?
- < 450 ms in men
- < 460 ms in women

What is concerning?
- QTc > 500ms
- Increase in QT > 60 ms
ARTERIAL HYPERTENSION

Preexisting HTN: 47%
Treatment with anti-hypertensive agent during therapy:
• At least 1 agent: 85% of patients
• At least 2 agents: 52% of patients

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Cardiac Medications Before/During Cancer Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>22%</td>
</tr>
<tr>
<td>Initiation or dose increase with treatment</td>
<td>24%</td>
</tr>
</tbody>
</table>

PERIPHERAL VASCULAR DISEASE

- Nilotinib
- Ponatinib

- Atherosclerotic and non-atherosclerotic PAD in LE: up to 30%

- L-asparaginase
- Cisplatin
- Methotrexate
- 5-FU
- Paclitaxel

- Radiotherapy:
  - Mediastinal
  - Cranial
- Double risk of stroke

Cranial
- Carotid stenosis
- Ischemic upper limb symptoms

Vascular Toxicity With BCR-ABI TKIs

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
<th>Peripheral Arterial Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>CVA/TIA, carotid artery disease</td>
</tr>
<tr>
<td>Supraclavicular and mediastinal radiation</td>
<td>CVA/TIA, carotid, and subclavian arterial disease</td>
</tr>
<tr>
<td>Abdominal and pelvic radiation</td>
<td>Renal arterial disease, lower extremity PAD</td>
</tr>
</tbody>
</table>

LEARNING OBJECTIVES

1. Explain the foundation and the medical need for cardio-oncology program within cancer center.
2. Describe cardiology challenges facing cancer patients and survivors.
3. Identify strategies to minimize long term cardiac toxicities and events for oncology patients.
**MYOCARDIAL DYSFUNCTION AND HEART FAILURE**

**DIAGNOSTIC TOOLS**

<table>
<thead>
<tr>
<th>Diagnostic Tool</th>
<th>Current Diagnostic Criteria</th>
<th>Advantages</th>
<th>Major Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECHO</strong></td>
<td>LVEF &gt; 10% points decrease to a value below lower limit of normal</td>
<td>Wide availability, lack of radiation, assessment of cardiac situations</td>
<td>Inter-observer variability, GLS inter-vendor variability, technical requirements</td>
</tr>
<tr>
<td><strong>MUGA</strong></td>
<td>LVEF &gt; 10% points decrease to a value &lt;50%</td>
<td>Identifies patients with cardiotoxicity, reproducibility</td>
<td>Cumulative radiation exposure, limited structural and functional information</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Typically used if other techniques are non-diagnostic or to confirm presence of LV dysfunction if LVEF is borderline</td>
<td>Accuracy, reproducibility, detection of diffuse myocardial fibrosis</td>
<td>Limited availability, patient adaptation (claustrophobia, breath hold, acquisition time)</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td>Troponin I, BNP, NT-proBNP</td>
<td>A rise identifies patients receiving anthracyclines who may benefit from early therapy</td>
<td>Accuracy, reproducibility, high sensitivity</td>
</tr>
</tbody>
</table>

**TRADITIONAL MUGA SCAN - DOWNSIDE**

1. Radiation-absorbed doses to the critical organs:
   - Adrenals: 8 mGy
   - Heart: 18 mGy
   - Kidneys: 14 mGy
   - Liver: 10 mGy
   - Spleen: 11 mGy

2. Cannot be used for the accurate evaluation of right ventricular function.

3. Incorrect gating due to variability in heart rate: frequent premature ventricular contractions and atrial fibrillation.

4. Inadequate labeling of erythrocytes with a reduced target-to-background ratio.

**BIOMARKERS**

**CARDIAC BIOMARKERS - TROPONIN**

- Elevated in 21% - 40% of patients after anthracycline chemotherapy, irrespective of assay type.
- May quantify both cardiomyocyte apoptosis and myofibril degradation more than necrosis.
- Predicts cardiotoxicity as well as major adverse cardiovascular events.
- Baseline levels may be elevated due to the burden of malignant disease itself.
TROPONIN

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

- 703 patients
- Tnl was measured soon after chemo and 1 month after
- Clinical + LVEF evaluation: 1, 3, 6, 12 months during treatment
- Q6 months after treatment for 3 years
- Exclusion criteria: age>70 years, LVEF <50%, heart, renal or hepatic disease


MYOCARDIAL STRAIN (GLS)

- Local shortening, thickening, and lengthening of the myocardium
- Measure of regional LV function
- Used to identify sub-clinical LV dysfunction in cardiomyopathies
- Expressed as a percentage.

GLS - PROSPECTIVE OBSERVATIONA STUDY

- 158 patients with breast cancer on ANT > 240mg/m² w/out adjuvant immunotherapy b/w June 2011-October 2015.
- Mean age - 54.6 +/- 12.9 years.
- Patients with heart disease or abnormal ECHO were excluded.
- Mean follow up - 5.4 months.
- All patients had at least 2 ECHO's, with a mean of 3.6 exams at a mean interval of 107 days.

Portugal et al. Rev.Port.Cardiol.2017

STUDY RESULTS

The mean period b/w worsening GLS and development of CIC - 103 days

GLOBAL LONGITUDINAL STRAIN (GLS)

Reduction in GLS of 10-11% at 3 or 6 months during treatment predicts subsequent cardiotoxicity in women treated with trastuzumab w/out anthracyclines for breast ca.

Portugal et al. Rev.Port.Cardiol.2017
PREVENTION STRATEGIES

Beta-blockers
ACEIs and ARBs
Aldosterone antagonists
Combination therapy
Dextrazoxane
Statins
Natural antioxidants

WHY BETA-BLOCKERS AND WHICH ONE?

Carvedilol
• Blocks Beta1, Beta2, Alpha – adrenoreceptors
• Decrease free radical release and apoptosis
• Does not decrease effectiveness of antineoplastics

Nebivolol
• Beta – selective antagonist
• Vasodilatory effect mediated by NO release

Metoprolol
• B1 – selective antagonist
• Neutral

Propranolol
• Blocks Beta1, Beta 2, Alpha –adrenoreceptors
• Might be harmful

80 females with breast cancer
Carvedilol group (12.5mg po daily for 6 months) vs Control group
Cumulative ANT dose - 523 mg/m^2
ECHO at baseline and after completion of therapy


WHAT DID WE LEARN?

RESULTS
• Strain and strain rate values - significantly decreased in control group after 6 months of ANT therapy.
• Protective effect in the short-term because of short-term follow up.

CONCLUSION
• Protective effect of the carvedilol can be detected more sensitively by strain.
• Carvedilol during ANT therapy preserves several subtle abnormalities in myocardial function that were detected in the asymptomatic period and normal EF.
• Function of some myocardial segments may be compensatory for dysfunctional segments leading to the preserved LVEF in the early stages of cardiotoxicity.

LIMITATIONS: open label, small sample size.


COMBINED THERAPY – “OVERCOME” TRIAL, 2013

90 patients with normal LVEF and newly diagnosed haematological malignancy were randomised to either enalapril + carvedilol (n=45) or control (n=45).

Patients: AML - 30, ALL - 6, 54 were undergoing autologous stem cell transplant for Hodgkin disease (n = 9), non-Hodgkin lymphoma (n = 23), and MM (n = 22).

Elitok et al. JACC, Vol 61, 2013

OVERCOME TRIAL – STUDY DESIGN

• Doses of enalapril and carvedilol were similar to heart failure studies.
• ECHO and CMR imaging studies were performed before and at 6 months after randomization.
• The primary efficacy endpoint was the absolute change from baseline in LVEF.
• The mean age of patients was 50+-13 years, 43% - women.

Bosch et al. JACC, Vol 61, 2013
OVERCOME TRIAL - RESULTS

Bosch et al. JACC, Vol 61, 2013

STUDY POPULATION (99 women)
All trastuzumab, 12-33% - anthracycline

STUDY DESIGN
1:1:1 bisoprolol (2.5mg), perindopril (5mg), placebo

PRIMARY OUTCOME – CMR
LVEDVi changes at 1 year

RESULTS
Attenuation of LVEF decline with bisoprolol (order of 4%)

PRADA
Decline in LVEF from baseline to end of study: -0.8% in the candesartan group vs. -2.6% in the placebo group (p = 0.026 for between-group difference)

Metoprolol was not associated with a change in LVEF vs. placebo

RESULTS
Conclusions
• Among women with breast cancer undergoing anthracycline chemotherapy, candesartan was effective at preserving LVEF
• Metoprolol succinate was not effective at preserving LVEF

Presented by Dr. Geeta Gulati at AHA 2015

MANTICORE

Placebo controlled, multicenter, double-blinded

Results
Decline in LVEF from baseline to end of study: -6.5% at 6 weeks vs. placebo (p = 0.007)

Conclusions
• MANTICORE: Women with breast cancer undergoing chemotherapy and/or radiation were randomized by factorial design to metoprolol succinate (target dose 100 mg daily) vs. placebo and to candesartan (target dose 32 mg daily) vs. placebo.

Presented by Dr. Geeta Gulati at AHA 2015

PRADA
Decline in LVEF from baseline to end of study: -6.5% at 6 weeks vs. placebo (p = 0.007)

Conclusions
• MANTICORE: Women with breast cancer undergoing chemotherapy and/or radiation were randomized by factorial design to metoprolol succinate (target dose 100 mg daily) vs. placebo and to candesartan (target dose 32 mg daily) vs. placebo.

Presented by Dr. Geeta Gulati at AHA 2015

RESULTS

<table>
<thead>
<tr>
<th>Placebo (N=30)</th>
<th>Perindopril (N=33)</th>
<th>Bisoprolol (N=31)</th>
<th>ANOVA P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre LVEDVi (mL/m²)</td>
<td>76 ± 13^*</td>
<td>67 ± 14</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>Post LVEDVi (mL/m²)</td>
<td>79 ± 12</td>
<td>74 ± 16^*</td>
<td>76 ± 14^*</td>
</tr>
<tr>
<td>∆ LVEDVi from baseline</td>
<td>+4 ± 11</td>
<td>+7 ± 14</td>
<td>+8 ± 9</td>
</tr>
<tr>
<td>Pre LVEF (%)</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>Post LVEF (%)</td>
<td>56 ± 4^*</td>
<td>59 ± 6^*</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>∆ LVEF from baseline</td>
<td>-5 ± 5</td>
<td>-3 ± 4</td>
<td>-1 ± 5^*</td>
</tr>
</tbody>
</table>

Trastuzumab interruptions due to drop in LVEF
8^* 1 1 0.002

Presented by Dr. Geeta Gulati at San Antonio Breast Cancer Symposium, 2015

FOR EFFECTIVE CARDIOPROTECTION TIMING IS A KEY...
ANTHRACYCLINE ALGORITHM

CARDIO-ONCOLOGY EVALUATION

- LVEF < 50%
- LVEF drop > 10%
- and abnormal strain

Chemotherapy
Hold Anthracyclines
Reassess in 1 month

ANTHRACYCLINE ALGORITHM

CARDIO-ONCOLOGY EVALUATION

- LVEF < 50%
- LVEF drop 

Chemotherapy
Hold Anthracyclines
Reassess in 1 month

TRASTUZUMAB ALGORITHM

CARDIO-ONCOLOGY EVALUATION

- LVEF < 50%
- LVEF drop

Chemotherapy
Hold Trastuzumab
Reassess in 3 wks

CORONARY ARTERY DISEASE

- Identify patients with pre-existing CAD.
- Pre-existing CAD increases risk of treatment related CAD.

- Radiation is significant risk factor.
  - Long latent period (10 years).
  - Presentation is atypical.

- Prevalence of silent ischemia is high.
- Concomitant neurotoxicity of radiotherapy.
- Chemotherapy affecting perception of angina.

- Sudden cardiac death is 2/2 left main stenosis.

- 2 fold increased risk of CAD after treatment for testicular cancer.

SCAI EXPERT CONSENSUS STATEMENT – CV SCREENING AFTER RADIATION THERAPY

- Define Cardiac Risk
  - Age > 55 or < 55
  - Woman or left anterior radiation
  - Presence and extent of further lesions in the heart
  - Lack of atherosclerosis
  - High HR (65+)
  - Prior MI or high risk MI
  - Prior radiation to heart
  - Prior CRT
  - Current smoking

- Additional risk factors
  - High BP
  - DM
  - Hypercholesterolemia

SCAI EXPERT CONSENSUS STATEMENT: INTERVENTIONS FOR CANCER PATIENTS WITH THROMBOCYTOPENIA

- Time to treatment
  - Within 7 days
  - Within 14 days

- Pre-procedural risk factors
  - Age > 65
  - Paroxysmal atrial fibrillation
  - Important comorbidities
  - Pre-existing CAD

- Clinical risk factors
  - Age > 65
  - DM
  - Hypercholesterolemia
  - Hypertension

Iliescu et al. Catheterization and Cardiovascular Interventions (2015)
**No minimum platelet count to perform a diagnostic coronary angiogram.**

**DAT with Plavix may be used with platelet counts 30,000-50,000/mL.**

**Prasugrel, ticagrelor, and IIB-IIA inhibitors should not be used with platelet counts <50,000.**

**PERIPHERAL ARTERIAL DISEASE – QUESTIONS TO ASK**

- What can be predicted by ABI?
- Does a normal test exclude risk?
- Does an abnormal test prohibit therapy?
- Which additional tests should these patients have?
- Should this be done routinely?
- How to respond to screening?
- How to evaluate and pursue prevention?

**PULMONARY HYPERTENSION**

**Dasatinib**
- 8-40 months after exposure.
- Reversible after discontinuation or replacement with another TKI.

**Cyclophosphamide**
- Pulmonary veno-occlusive disease.
- Most severe form of pulmonary hypertension.
- Asymptomatic patients – assess level of PAP pressure – how often?
ADDITIONAL CONSIDERATIONS

- Identification of patient group that would derive the greatest benefit is important from risk-benefit and cost-effectiveness standpoint.

- Precinical identification of LV dysfunction is crucial, as early therapy might allow complete recovery and no interruption in cancer therapy.

- Genetic predisposition and pharmacogenetic testing.

- Individualized dosing selection.

MORE TO COME

SUCCOUR TRIAL - Strain surveillance during Chemotherapy for improving Cardiovascular Outcomes Trial

- First large-scale, international randomized study of chemotherapy patients at risk of cardiotoxicity.

- 12 countries, including U.S. centers.

- Enrollment started in 2014 and will follow for three years.

SENeca TRIAL - Cardiac progenitor cells

An iceberg conveys what we know (shown above the water) and don’t yet know (below the water) about cardiovascular and cardio-metabolic toxicities of cancer treatments.

References (1)


References (2)


