Cardiovascular Considerations during Bone Marrow Transplantation

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Presenter Disclosure Information

BMT Tandem Meeting: San Diego CA, 2/2015

I will not discuss off label use or investigational use in my presentation.

I have financial relationships to disclose:

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- **Consultant (modest): Roche, Onyx, Incyte**

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Cardiovascular (CV) Considerations during Bone Marrow Transplantation (BMT)

Objectives:

- Describe common cardiovascular issues encountered during BMT
- Identify high risk populations for cardiac complications during transplant
- Explain strategies to minimize complicating medical issues
- Recognize current clinical research gaps and discuss proposals for ongoing projects

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Cardiovascular Considerations during BMT
Potential serious cardiac complications

- QT prolongation/Rhythm disturbances
- Heart Failure
- Myocardial injury
- Endovascular Infection

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Cardiovascular Considerations during Bone Marrow Transplantation

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What is the best CV recommendation in preparation for BMT? A case story

- 66 y/o M, with previous coronary disease (CAD) and aortic valve replacement (AVR) in 2006 developed NH lymphoma, initially diagnosed in 1/2012
- He was initially treated with anthracycline based therapy for 4 cycles
- He tolerated this until he had heart failure (HF) and a resultant left ventricular ejection fraction (LVEF) of 35%
- Achieved remission at 4 cycles

2/4/2015

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Case study (cont'd)

- **Past hx:** Hypertension (HTN), hyperlipidemia, CAD s/p bypass x3 with AVR on carvedilol 6.25mg bid, atorvastatin 40 mg, aspirin, furosemide 40mg, and lisinopril 20mg.
- 3 months after chemo, he developed chest pain and reportedly got a drug eluting stent in the right coronary artery (8/2012)
- He was then seen in December 2012 and was asymptomatic
- Now he has recurrent disease, received 2 cycles of non-anthracycline based therapy (RICE), and is potentially getting a stem cell transplant

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Physical Exam and Labs

- 124/77, HR 61, R 18, afebrile
- Jugular venous pressure (JVP) 8 cm. Lungs: few basilar crackles. Cardiac exam: loud S4, PMI enlarged
- No edema, good distal pulses

- Na 136, Cr .9, Cl 21.
- Hgb 11.5, plt 216, LDL 74
- B-type natriuretic peptide (BNP) 107, trop I 0.01

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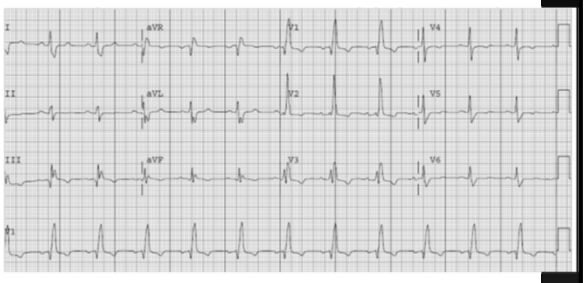
ECG Now



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Echocardiography and BNP over time

- Echo 5/2013:
  AV velocity 3.1 m/sec
  LVEF 45-50%
- Previous echos:
  - 1/12 LVEF 60
  - 2/12 LVEF 53
  - 4/12 LVEF 35
  - 7/12 LVEF 20
  - 8/12 LVEF 34
  - 2/13 LVEF 45-50
- BNP
  - 327 (12/2012)
  - 147 (2/2013)
  - 107 (5/2013)
  - 296 (6/2013)

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So what is the best recommendation?

- Further Pre-BMT evaluation?
- Stop clopidogrel, aspirin?
- Go ahead and take your shot?

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What is the risk of a drug eluting stent prior to a procedure?

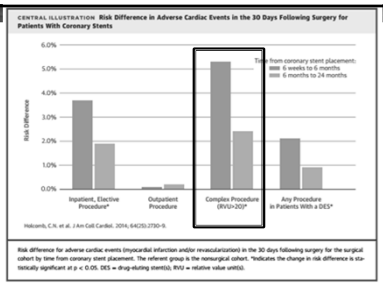

TABLE 4 Adverse Cardiac Events and All-Cause Mortality and Risk Differences in the Post-Stent Cohort Undergoing Surgery Versus the Matched Nonsurgery Cohort During the Matched 30-Day Interval, Stratified by Time From Coronary Stent Placement

	≤6 Weeks (n = 3203)		6 Weeks to 6 Months (n = 15,698)		>6 Months to 24 Months (n = 40,198)	
Event	Event, %	Risk Difference, % (95% CI)*	Event, %	Risk Difference, % (95% CI)*	Event, %	Risk Difference, % (95% CI)*
Composite cardiac†	9.0	2.8 (0.8 to 4.8)	4.6	2.0 (1.3 to 2.7)	2.3	0.9 (0.7 to 1.2)
MI	7.5	3.6 (1.8 to 5.4)	3.8	2.2 (1.6 to 2.8)	1.8	1.0 (0.8 to 1.2)
Revascularization	2.7	−0.1 (−1.3 to 1.1)	1.5	0.0 (−0.5 to 0.4)	0.8	0.0 (−0.1 to 0.3)
All-cause mortality	3.2	2.5 (1.4 to 3.6)	2.1	1.4 (0.9 to 1.9)	1.1	0.8 (0.7 to 1.0)

*Risk difference reflects difference between the surgical cohort and the matched nonsurgical cohort following coronary stent placement. †Postoperative acute MI and/or revascularization with coronary artery bypass grafting or coronary stent placement.
MI = postoperative acute myocardial infarction.

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Biol Blood Marrow Transplant 17:1182-1186, 2011

Table 5. Proportion of Comorbidities between CAD and Control Groups

Comorbidities	CAD (%)	Control (%)	*P* Value
Diabetes	14 (20.3)	97 (8.7)	.004
Hypercholesterolemia	39 (56.5)	256 (23.1)	<.001
Smoking	37 (53.6)	467 (42.1)	.078
Hypertension	29 (42.0)	377 (34.0)	.192

CAD indicates coronary artery disease.

Table 6. Outcomes of HSCT for CAD and Control Groups

Variable	CAD (%)	Control (%)	*P* Value
Death during transplantation	4 (5.6)	58 (4.9)	.777
Death to 1 year	11 (15.3)	196 (16.6)	.871
ICU admission	8 (11.1)	117 (9.9)	.686
Length of stay ± SD (years)	25.53 ± 11.18	28.42 ± 18.72	.195
Cardiac events	7 (9.7)	59 (5.0)	.096

CAD indicates coronary artery disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit.

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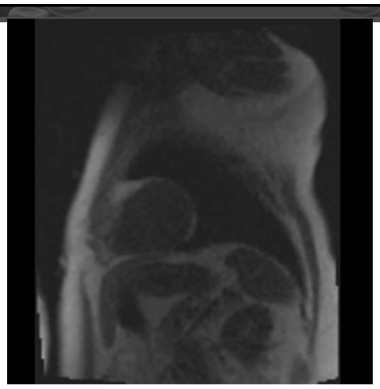

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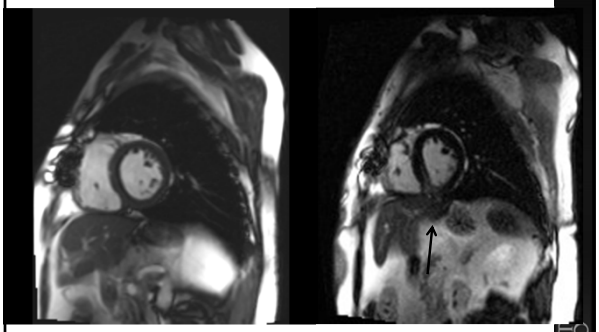

LVEF 38%; RVEF 42%

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What do you say now?

- Is he stable to proceed?
- How risky is this BMT?
- Would you do anything else?
  - Consider dental evaluation

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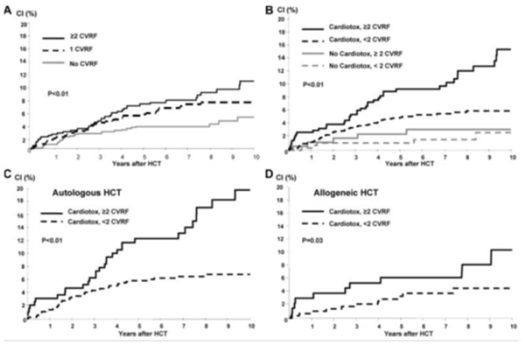
Pre-stem cell risk factors are very important



Armenian, S. Blood. 2012 Nov 29;120(23):4505-12. doi: 10.1182/blood-2012-06-437178. Epub 2012 Oct 3.

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Cardio-Oncology: How do we manage co-morbidities during BMT?

- 64 y/o with myeloma and amyloidosis (cardiac involvement) who is being treated with bortezomib, lenalidomide for 6 months (on maintenance now) and has achieved a remission
- He is being considered for an autologous BMT

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Case 2: Myeloma with amyloid

- PMH: HTN, hyperlipidemia, chronic kidney disease, HF, CAD, AV nodal re-entry tachycardia with AV nodal ablation
- Deep venous thrombosis, sleep apnea
- Meds: carvedilol 6.25mg bid, aspirin, pravastatin 20mg, allopurinol, furosemide

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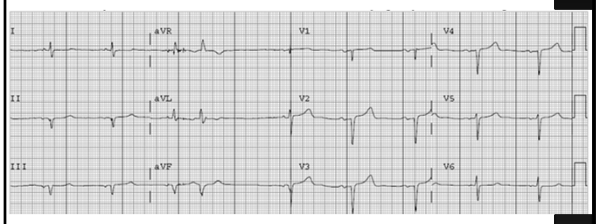
Current ECG



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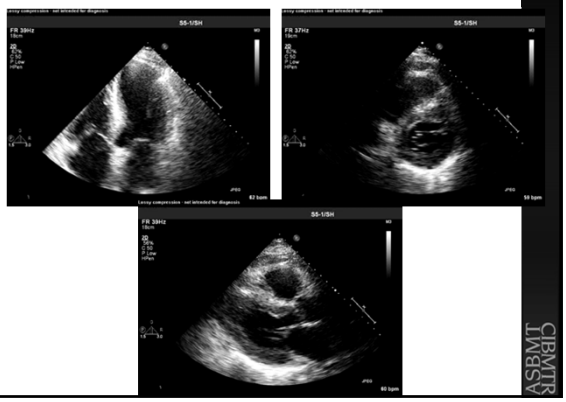
Recent Echo



Case 2: Phys Exam and Labs

- BP 130/78, P70
- 8-9 cm JVP, lungs clear, loud S4, 1+ edema
- BUN/Cr 58/2.0, trop I 0.09, BNP 221
- Maximal oxygen consumption (MVO2) = 12.7
- Recent cath: 40-60% circumflex, 30-40 % right coronary artery
- Right heart cath: Pulmonary artery 44/20 mm Hg, mean wedge 22, Fick cardiac index 2.71 (CO=6.4 l/min)

BMT and CV Issues: How do we manage these?

- So what are the effective pre-op evaluations?
- Can he be optimized better?

The further reduced the cardiac output, the worse the arrhythmia risk

Goldsmith, et al, Am J Cardiol 2009;104:990 –994

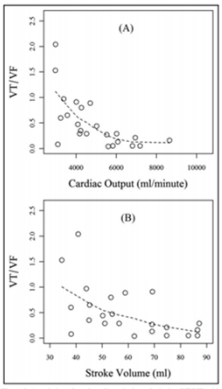


Figure 1. Association of number of ventricular arrhythmias (VT/VF) with (A) cardiac output ($p < 0.0001$) and (B) stroke volume ($p = 0.0029$).

Biomarkers may be helpful in identifying developing toxicity

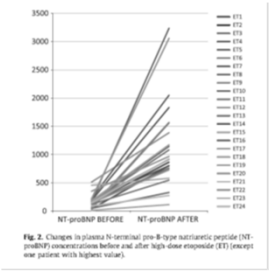


Fig. 2. Changes in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations before and after high-dose etoposide (ET) (except one patient with highest value).

Table 3
Factors associated with the elevation of plasma NT-proBNP – univariate analysis.

	p Value
Age	0.87
Sex	0.9
Underlying disease	**0.002**
Number of chemotherapy regimens	0.054
Cumulative anthracycline dose	**0.008**
GFR at the time of mobilization	0.236
Mobilization chemotherapy	**0.001**

GFR = Glomerular filtration rate.

Ozkan, H A, et al Transfusion and Apheresis Science 2013

Prevention of Cardiotoxicity is possible

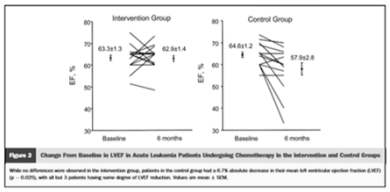


Figure 2 Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

While no differences were observed in the intervention group, patients in the control group had a 6.7% absolute decrease in their mean left ventricular ejection fraction (LVEF) ($p < 0.05$), with all but 3 patients having some degree of LVEF reduction. Values are mean ± SEM.

Table 4 Clinical Endpoints

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF <45% (%)	3 (6.7)	11 (24.4)	0.020
≥10% decrease in LVEF with a final LVEF <50% (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or ≥10% decrease in LVEF (%)	4 (9.5)	7 (19)	0.22
Severe adverse events* (%)	9 (20)	15 (33)	0.15

Values are n (%). *Defined as a serious adverse event that resulted in death or was life-threatening.
LVEF = left ventricular ejection fraction.

Bosch, X et al, JACC 2013, p 2355

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TABLE 1. Characteristics of Late-Occurring CVD in HCT Survivors

Characteristic	Arterial Disease	Cardiac Disease
Cardiovascular complications	• Cerebrovascular disease (stroke, transient ischemic attack, cerebral arterial occlusion, symptomatic lacunar infarctions) • Coronary artery disease (myocardial infarction, atherosclerotic heart disease, angina pectoris)	• Cardiomyopathy, congestive heart failure • Constrictive pericarditis • Valvular heart disease • Conduction abnormalities
HCT recipients at highest risk	Survivors of allogeneic HCT	Survivors of autologous HCT
Median time to CVD from HCT, y	4-9	2-3
Median age at first CVD,y	48-54	50-52
Clinical risk factors	• Older age at HCT • Cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity)	• Female sex • Cardiovascular risk factors (hypertension, diabetes)
Pre-HCT therapeutic risk factors	• Radiation (cerebrovascular disease [cranial, cervical]and coronary artery disease [chest])	• Anthracycline chemotherapy • Radiation (chest)
HCT-related risk factors	• Graft-versus-host disease	–

Abbreviations: CVD, cardiovascular disease; HCT, hematopoietic cell transplantation

Armenian S, et al, Cancer 2014;120:469–79.

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Table 2 Cardiopulmonary Function and Functional Capacity Testing Data

Variable	Mean ± SD	Median (Range)
Data at rest		
Heart rate (beats/min)	78 ± 20	70 (50-130)
Systolic blood pressure (mm Hg)	123 ± 14	123 (94-150)
Diastolic blood pressure (mm Hg)	75 ± 9	76 (62-94)
Exercise peak		
Heart rate (beats/min)	145 ± 23	144 (109-184)
Predicted %, heart rate (beats/min)	91 ± 14	88 (67-120)
Systolic blood pressure (mm Hg)	167 ± 22	166 (128-204)
Diastolic blood pressure (mm Hg)	76 ± 12	76 (56-110)
VO_{2peak} (mL/kg/min)	17.5 ± 5.9	16.9 (8.0-31.4)
VO_{2peak} ≤14 mL/kg/min	6 (27%)	
Predicted %, VO_{2peak} (mL/kg/min)	62 ± 18	61 (33-104)
VO_{2peak} (L/min)	1510.9 ± 557.5	1470.4 (670.3-2710.2)
Workload (W)	109 ± 46	102 (41-220)
METs	5.0 ± 1.7	4.8 (2.3-9.3)
RER	1.16 ± 0.08	1.17 (1.03-1.28)
Functional capacity		
6MWD (m)	500.4 ± 91.9	522.5 (275-675)
Predicted %, 6MWD	75 ± 13	76 (43-98)

Data presented as mean ± SD for continuous data and n (%) for categorical data.
Abbreviations: 6MWD = 6-minute walking distance; METs = metabolic equivalent; RER = respiratory exchange ratio; VO_{2peak} = peak oxygen consumption.

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Patients with myeloma have marked and significant reductions in quantitative measures of physical function for years after the initial therapy

Tuchman, SA,et al, Clinical Lymphoma, Myeloma & Leukemia, 2014

Statin therapy prior to and during chemotherapy was protective

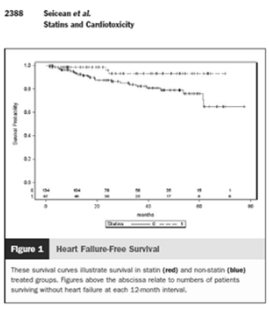
2388 Seicean *et al.*
Statins and Cardiotoxicity

Figure 1 Heart Failure-Free Survival

These survival curves illustrate survival in statin **(red)** and non-statin **(blue)** treated groups. Figures above the abscissa relate to numbers of patients surviving without heart failure at each 12-month interval.

JACC 2012, p 2384

Are there things on the cancer therapy horizon that could be concerning for cardiomyopathy?

There is a balance between protein synthesis and degradation

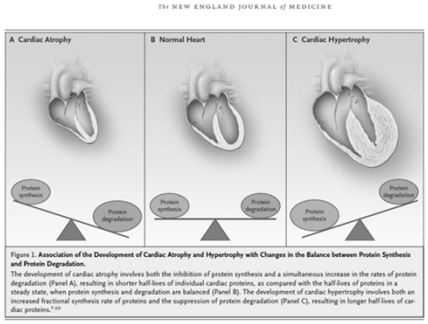

Figure 1. Association of the Development of Cardiac Atrophy and Hypertrophy with Changes in the Balance between Protein Synthesis and Protein Degradation.
The development of cardiac atrophy involves both the inhibition of protein synthesis and a simultaneous increase in the rates of protein degradation (Panel A), resulting in shorter half-lives of individual cardiac proteins, as compared with the half-lives of proteins in a steady state, when protein synthesis and degradation are balanced (Panel B). The development of cardiac hypertrophy involves both an increased fractional synthesis rate of proteins and the suppression of protein degradation (Panel C), resulting in longer half-lives of cardiac proteins.[1-10]

Monte S. Willis, M.D., Ph.D., and Cam Patterson, M.D., M.B.A.
NEJM 2013;368:455-64.

Properties of bortezomib and the second-generation proteasome inhibitors

Proteasome inhibitor	IC_{50} $\beta5/\beta2/\beta1$ (nM)	IC_{50} NF-κB (nM)	Dissociation $t_{1/2}$ (min)
Bortezomib	2.4–7.9/590–4200/24–74 [16,18,25]	36–40 [18,25,39]	110 [18]
MLN9708 [18]	3.4/3500/31	62	18
CEP-18770 [19,20]	3.8/>100/<100	NR	NR—slowly reversible
Carfilzomib [16]	6/3600/2400	NR	Irreversible
PR-047 [21]	36/NR/NR	NR	Irreversible
NPI-0052	3.5/28/430 [25]	13–20 [25,39]	Irreversible

Abbreviations: IV, intravenous; MCL, mantle cell lymphoma; MM, multiple myeloma; NR, not reported; SC, subcutan

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Carfilzomib CV Side Effects per USPI

- CHF, Decreased LV Ejection fraction 7%
- Pulmonary Edema 7%
- Cardiac Ischemia, ACS* <1%
- Cardiac Arrest resulting in Death 1%

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A report of 6 cases describing carfilzomib related cardiac dysfunction and the patterns of cardiotoxicity

	Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Carfilzomib Exposure	Dosing (mg/m²)	20x1 then 27	27	20	20	27	20x1 then 27
	Duration of Therapy (mos)	3	5	6	1	3	3
	Total Cumulative Dose (mg/m²)	405	903	972	141	540	444
Baseline	NYHA Class	I	I	I	I	I	I
	LVEF	50 – 55	60 – 65	55	55-60	58	68
	BNP (pg/mL)	N/A	79[†]	534[+]	N/A	N/A	N/A
	Troponin	N/A	N/A	< 0.05	N/A	N/A	N/A
With Carfilzomib	Worst NYHA Class	III	II	III	III	III	III
	Nadir of LVEF (%)	25 – 30	47	50	< 20	25 – 30	44
	Highest BNP or NT-proBNP[*] (pg/mL)	1837[†]	170[†]	2988[†]	2026	640	744
	Highest Troponin	< 0.05	< 0.05	< 0.05	2.5	0.01	< 0.05
Recovery	Carfilzomib Discontinuation	Permanent	Temporary	Permanent	Permanent	Permanent	Temporary
	Heart Failure Therapy Initiated	Beta-blocker; ACE-I; loop diuretic	None	Beta-blocker; ARB	Beta-blocker; ACE-I	Beta-blocker; aldosterone antagonist	Beta-blocker; aldosterone antagonist; loop diuretic
	Best NYHA Class	I	II	III	I	II	II
	Highest LVEF	40	50	55	50	48	68
	Lowest BNP (pg/ml)	65	104	2032	39	470	110
Summary of Cardiac Events		HF, LV dysfunction	Mild LV and RV dysfunction	HF	ACS, HF, QTc, LV dysfunction	HF, LV dysfunction	HF, LV dysfunction

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CV Considerations during BMT Conclusion

- Pre-stem cell assessment and medical optimization is crucial
- During BMT careful adjustment and monitoring can prevent major issues
- Risk factor modification after BMT is needed
- Collaboration among disciplines is the key

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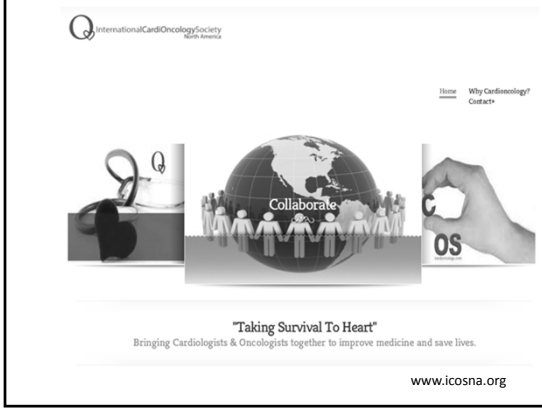

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Global Cardio-Oncology Summit

Event Details

Date: October 15-16, 2015

Location: The Hilton Nashville Downtown

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ARS Question #1

What major cardiac concerns are there when a patient undergoes BMT?

a. Arrhythmias/QT prolongation
b. Heart Failure
c. Myocardial injury
d. All of the above

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ARS Question #2

Identify which one of the major baseline cardiac risk factors for the development of cardiac events is least important:

a. Chest radiation
b. Prior anthracycline use
c. Hypertension
d. Coronary Disease

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ARS Question #3

Treatment with what cardiac medications is not beneficial before or during chemotherapy or bone marrow transplant ?

a. Clopidogrel
b. Atorvastatin
c. Enalapril
d. Carvedilol

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