Investigational Drug Steering Committee Update

Angiogenesis Task Force
Cardiovascular Toxicities Panel

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Angiogenesis Taskforce

Cardiovascular Toxicities Panel

- Formation
- Process
- Results

Angiogenesis Taskforce

“we need to do something about these adverse events and how to deal with them rationally” Scot Remick, 11/06

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"We think the future looks really bright for these drugs, but the way we deliver them is going to require teamwork," says co-organizer Dr. Jean-Bernard Durand of the Cardiomyopathy Service at M.D. Anderson.

"Good medical management with drugs already approved by the FDA for heart failure may solve a number of these issues," he adds.

The meeting was the first initiative of CONQUER (Cardiology Oncology International Quest to Educate and Research Heart Failure). The presidents of ASCO and the Heart Failure Society of America both participated.

"The issues of efficacy and toxicity go hand in hand," says Dr. Hortobagyi. "The best we can do is to assume that toxicities are going to occur and take all of the proper precautions without slowing down progress." ◆

Cardiovascular Toxicities Panel -Formation

Co-Chairs Angiogenesis Task Force: **George Wilding** **Roy Herbst**

AngiogenesisTask Force Members:

Helen Chen	**CTEP/NCI Liaison**
Percy Ivy	**CTEP/Past Co-Chair**
Glenn Liu	**U. Wisconsin/Imaging, GU Malignancies**
Michael Maitland	**U. Chicago/Clinical Pharmacology**
Scot Remick	**Case Western U01 PI (now U West Virginia)**

American Society of Hypertension Members:

George Bakris	**Director, Hypertension Unit U. Chicago**
Henry Black	**President, Professor NYU**
William Elliott	**Director, Hypertension Center, Rush University**

CONQUER/Heart Failure Society of America Members:

Jean-Bernard Durand	**MD Anderson Cancer Center**
Carl Leier	**Ohio State University Medical Center**
JoAnn Lindenfeld	**U. Colorado Medical Center**
Richard Steingart	**Memorial Sloan-Kettering Cancer Center**
Wilson W. H. Tang	**Cleveland Clinics**

NCI/EMMES: **LeeAnn Jensen** **Amy Gravell**

Cardiovascular Toxicities Panel -Process

Mission:

- To bring together experts in management of cardiovascular diseases and oncologists to discuss shared concerns of toxicities of VEGF signaling pathway inhibition therapy

- To report to ATF/IDSC on state of science in understanding mechanisms of adverse events, recommend areas for further research, provide guidance on standardized management of toxicities in future clinical trials

Cardiovascular Toxicities Panel -Process Blood Pressure Consensus Report

- **May – July ’07:**
  - initial telecon, writing teams formed (paired oncologists and CV specialists), initial outline presented and discussed on 7/12;
- **Sept – Nov ’07:**
  - consensus discussions on recommendations for initial evaluation and management of hypertension
- **Dec ’07 – Mar ’08:**
  - First draft Blood Pressure Consensus Report
- **Jul ’08 – Aug ’08:**
  - Report presented to and rec’s approved by IDSC

Cardiovascular Toxicities Panel -Results

Themes

- ***1)Cross-specialty education, on practice standards, epidemiology, terminology***
- ***2) "Wake up" cardiovascular specialties community to be more attentive/supportive to this increasingly critical issue***
- ***3)Alert and guide oncologists in more attentive supportive care, akin to nausea/vomiting/ infection risk management with cytotoxics***

Cardiovascular Toxicities Panel -Results

"The purpose of this project is to make safe for the greatest possible number of patients receipt of new anticancer agents that have associated cardiovascular toxicities."

Cardiovascular Toxicities Panel -Results

5 Reasons for Attentive BP Management During VEGF Signaling Pathway (VSP) Inhibitor Therapy:

1) Serious adverse events associated with unmanaged blood pressure elevations could be prevented

2) Magnitude of BP elevation is variable and as yet unpredictable

3) Potential benefits of more attentive co-morbidity management

4) As use expands to more and earlier disease settings, principles are increasingly the same as for primary care

5) Active control of hypertension should allow patients to tolerate highest dose for longest period, improving outcomes

Need to speak the same language

	Grade				
Short Name	1	2	3	4	5
Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric:	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric:	Requiring more than one drug or more intensive therapy than previously Pediatric:	Life-threatening consequences (e.g., hypertensive crisis) Pediatric:	Death

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial drug therapy: Without Compelling Indication	Initial drug therapy: With Compelling Indications (See Table 8)
Normal	<120	and <80	Encourage		
Prehypertension	120–139	or 80–89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

Cardiovascular Toxicities Panel 1-Results

4 Recommendations for BP Management During VSP Inhibitor Therapy :

1) Candidates for VSP inhibitor therapy should undergo a dedicated pre-treatment risk assessment

2) Goal BP is ≤ 140/90mmHg before and during treatment

3) BP should be measured accurately, early, and often

4) Most can have BP elevation managed by their oncologists, a subset will require care from a cardiovascular specialist

Recommendation #1
Pre-treatment risk assessment

Blood pressure (mmHg)					
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

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Recommendation #2
Goal BP is ≤ 140/90mmHg

1. In accord with current public health (NHLBI) guidelines (JNC 7)
2. Goal, not a mandate, adds a higher margin of safety than current practice seemingly focused on Grade 2 CTCAE threshold of 150/100 mmHg
3. Assessment & management of BP can be done by medical oncologists

Recommendations #3/4
Consulting a cardiovascular specialist

"If the oncologist or responsible medical team member has any difficulty in helping the patient progress to the goal blood pressure of 140/90 mmHg consultation with the local hypertension specialist (cardiologist, nephrologist, endocrinologist or certified hypertension specialist) should be obtained promptly"

Guidance for the oncologist managing BP

Considerations for appropriate antihypertensive

1) cancer and cancer therapeutics-specific cautions and contraindications to avoid a specific agent
2) compelling considerations for preferring a specific agent in the general medical setting
3) cautions and contraindications to avoid a specific agent in the general medical setting
4) time available to titrate to goal effect

Future Directions

- Second Consensus Report- Cardiac Toxicities
  - Began 8/08, led by Richard Steingart MSKCC
  - New experts joined: Daniel Lenihan MDACC,

  Ming-Hui Chen DFHCC, Thomas Force Thomas Jefferson MC
- Blood Pressure Consensus Report
  - planned publication
  - available by request
  - will be integrated into CTEP-sponsored trials of VSP inhibitors
- Expert advisory group- opportunity for new collaborative efforts-
  - eg. 2 panel members joined CTCAE v.4 project
  - Stimulated similar efforts in PI3K/Akt/mTOR Subgroup 3

Challenges

- “orphan” academic and investigational interest
- voluntary effort
- data-poverty

Table 5: Cautions, contraindications, compelling considerations

Class of drug	Cancer-specific cautions/reasons to avoid	Basis for preferred selection	General cautions and contraindications
Angiotensin converting enzyme inhibitors	•Co-administration/ titration with renal clearance-dependent agents (eg. cisplatin, pemetrexed) •Hyperkalemia	•Left ventricular systolic dysfunction •Diabetic nephropathy	•Renovascular disease •Peripheral vascular disease •Renal impairment
Angiotensin II receptor blockers	•Co-administration/ titration with renal clearance-dependent agents (eg. cisplatin, pemetrexed) •Hyperkalemia	•Intolerance of other agents, especially ACE inhibitors •Left ventricular systolic dysfunction •Diabetic nephropathy	•Renovascular disease •Peripheral vascular disease •Renal impairment
β blockers	•Asthenia •Malaise •Fatigue	•Angina •History of myocardial infarction •Anxiety	•Bradycardia/heart block •Diabetes (risk for hypoglycemia) •Asthma/COPD (wheezing) •Decompensated heart failure
Calcium channel blockers (dihydropiridines)	•Lower extremity swelling	•Elderly patients •Isolated systolic hypertension	----------
Thiazide diuretics	•Gout •Hypercalcemia •Hypokalemia •Young patients (age $\leq$ 45)	•Elderly patients •Isolated systolic hypertension •Secondary stroke prevention •Typically least expensive	•Gout •Documented sulfa allergy