Clinical management of hypertension induced by treatment with angiogenesis inhibitors

Prof Jean-Philippe Spano
Dr Thibault de La Motte Rouge
Service d’oncologie médicale, Hôpital Pitié Salpêtrière
Paris, France
Learning objectives

• Understand the mechanisms of hypertension (HTN) induced by angiogenesis inhibitors

• To know the risk factors and the frequency of HTN induced by angiogenesis inhibitors

• Understand the keypoint of treatment of HTN induced by angiogenesis inhibitors
Angiogenesis

- Angiogenesis: development of new blood vessels from existing vasculature
- Central Hypothesis - any increase in tumor size must be preceded by an increase in tumor vasculature. This increase in tumor vasculature is stimulated by the tumor.
Angiogenesis inhibitors (AI): A new frontier in cancer therapy

- Angiogenesis is critical for the development and subsequent growth of human tumors

- VEGF exerts its activity by binding to several high-affinity transmembrane endothelial cell receptors (VEGFRs)

- But: VEGF also plays a role in physiological processes, such as wound healing and in many tissues (mucosal integrity, female reproductive cycle, etc.)

- AI lack the typical and often cumbersome side-effects of cytotoxic agents, but are not devoid of toxicity
Antiangiogenic agents: Cardiovascular side effects

- Hypertension and cardiovascular events:
  - Hypertension: the most prominent
    - VEGF regulates vasomotor tonus and maintains blood pressure, induces decrease blood pressure by dilating small arterioles and venules
  - Arterial thrombotic events
  - Ventricular dysfunction

- Hypertension: consequences of anti-VEGF ⇒ reduced density of micro-vessels

- Hypertension is often associated with proteinuria, cardiovascular events and bleeding
Hypertension: Risk factor of cardiovascular toxicity

- Anticancer agents that target VEGF pathway increase blood pressure

- High blood pressure = risk factors for
  - coronary heart disease
  - stroke
  - heart failure
  - end-stage renal disease

- High blood pressure: manageable side effect
  - multiple different drugs could be used as treatment
Normal blood pressure regulation

• **Blood volume regulated by kidney**: renin-angiotensin-aldosterone system

• **Vascular resistance regulated by**
  • sympathetic (alpha- and beta-adrenergic systems) and parasympathetic (vagal nerve) control
  • Autoregulation of myogenic activity in blood vessels by release of nitric oxide (NO): vasodilatation

• **Blood flow as a result of cardiac output** (heart rate x stroke)
Normal blood pressure regulation

↑ Blood volume

leads to

↑ Blood Pressure

Fast response

Compensation by Cardiovascular System

Vasodilation

↓ Cardiac output

Compensation by kidneys

Excretion of fluid in urine

↓ Blood volume

Blood pressure to normal
Renin angiotensin system and VEGF

- **Angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor antagonist**
  - cytostatic effect on cell line culture
  - delay tumor growth in animals
  - reduce incidence and delay growth of tumors in patients as compared to alternate medication (retrospective data)

- **Angiotensin II**
  - powerful mitogen
  - Regulates apoptosis and angiogenesis

Molteni A et al. Med Chem 2006 Sep;6(5):451-60
Renin-angiotensin pathways and VEGF expression

AT1

tubule lumen

Apical membrane

Epithelial cell

AGT Ang I Ang II renin ACE

ERK

VEGF

AGT: angiotensinogen; ANG: angiotensin; ACE: angiotensin-converting enzyme; ERK: extracellular-activated kinase

Adapted from Feliers et al. Mol Cell Endocrinol 2010, Jan, 15; 314(1): 136-42
VEGF/VEGFR2 signaling: Vasodilatation via NO production

- Blockage of VEGF leads to vasoconstriction

- VEGFR2 signaling generates nitric oxyde (NO) and prostaglandin I₂
  - vasodilatation endothelial cell dependent in arterioles and venules

- Blockade of VEGFR2 signaling reduces NO synthase expression and NO synthesis
Hypertension: Definition according to JNC7 classification

- **Normal**
  - systolic blood pressure (SBP) < 120 mmHg
  - diastolic blood pressure (DBP) < 80 mmHg

- **Prehypertension**
  - SBP from 120 to 139 mmHg
  - DBP from 80 to 89 mmHg

- **Hypertension**
  - Stage 1: SBP 140 – 159 or DBP 90 – 99 mmHg
  - Stage 2: SBP ≥ 160 mmHg or DBP ≥ 100 mmHg
Direct vascular effect of VEGF/VEGFRs targeting agents

VEGF inhibition

NO down-expression  Vascular rarefaction

Increase in vascular resistance

Hypertension


Nixon A. JCO 2007, ASCO, Abstr 14039

but hypertension may also result from VEGF/VEGFRs inhibition in the kidney ...
Renal expression of VEGF and VEGFRs
Mechanism of hypertension (HTN) induced by angiogenic inhibitors

VEGF inhibitors

↓ VEGF activity

Endothelial cells

Vascular rarefaction

NO down-expression

↓ Vascular resistance

Renal endothelial cells and podocytes

Dysregulation of VEGF expression

↓ Down-regulation of tight junctions proteins

HTA

Proteinuria
**Hypertension grading and therapeutic recommendation: Comparison between NCI (CTCv3.0) and JCNC7**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Hypertensive AE and recommendation</th>
<th>Class</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>Normal SBP Prehypertension</td>
<td>Requiring treatment in high cardiovascular risk patients</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic, transient (&lt;24 hrs) increase by &gt;20 mmHg (diastolic) or to &gt;150/100 if previously WNL; Intervention not Indicated</td>
<td>Normal SBP Prehypertension</td>
<td>Requiring treatment in high cardiovascular risk patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage I hypertension</td>
<td>Treatment required</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent or persistent (≥24 hrs) or symptomatic increase by &gt;20 mmHg (diastolic) or to &gt;150/100 if previously WNL; Monotherapy may be indicated</td>
<td>Stage 1 hypertension</td>
<td>Treatment required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stage 2 hypertension</td>
<td>Treatment required</td>
</tr>
<tr>
<td>3</td>
<td>Requiring more than one drug or more intensive therapy than previously</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (e.g., hypertensive crisis)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* JNC 7 Blood Pressure Classification for Adults [Chobanian AV, Hypertension 2003]: Normal SBP < 120 and DBP<80 mmHg; Prehypertension SBP 120-139j or DBP 80-89 mmHg; Stage 1 hypertension SBP 140-159 or DBP 90-99 mmHg; stage 2 hypertension SBP ≥ 160 or DBP ≥ 100 mmHg

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th>Regimen</th>
<th>Patient, n</th>
<th>Hypertension, % All grade/ Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCRC</td>
<td>Hurwitz et al</td>
<td>IFL</td>
<td>397</td>
<td>8.3/2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFL + beva 5mg/kg</td>
<td>393</td>
<td>22.4/8.3</td>
</tr>
<tr>
<td></td>
<td>Hurwitz et al</td>
<td>Placebo + IFL</td>
<td>98</td>
<td>14.3/3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5FU + leucovorin+beva 5mg/kg</td>
<td>109</td>
<td>33.9/18.3</td>
</tr>
<tr>
<td></td>
<td>Giantonio et al</td>
<td>FOLFOX4</td>
<td>285</td>
<td>NA/1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOLFOX4 + beva 10 mg/kg</td>
<td>287</td>
<td>NA/6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beva 10 mg/kg</td>
<td>234</td>
<td>NA/7.3</td>
</tr>
<tr>
<td>mRCC</td>
<td>Escudier et al</td>
<td>Placebo + INFα</td>
<td>322</td>
<td>9/1&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beva 10 mg/kg + INFα</td>
<td>327</td>
<td>26/3</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Sandler et al</td>
<td>CBBD + paclitaxel</td>
<td>444</td>
<td>NA/0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBBD + paclitaxel + beva 15 mg/kg</td>
<td>444</td>
<td>NA/7</td>
</tr>
<tr>
<td></td>
<td>Reck et al</td>
<td>CDDP + gemcitabine + placebo</td>
<td>327</td>
<td>NA/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDDP + gemcitabine + beva 7.5 mg/kg</td>
<td>330</td>
<td>NA/6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDDP + gemcitabine + beva 15 mg/kg</td>
<td>329</td>
<td>NA/9</td>
</tr>
<tr>
<td>mBC</td>
<td>Miller et al</td>
<td>Capecitabine</td>
<td>215</td>
<td>2.4/0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capecitabine + beva 15 mg/kg</td>
<td>247</td>
<td>33.5/17.9</td>
</tr>
<tr>
<td></td>
<td>Miller et al</td>
<td>Paclitaxel</td>
<td>346</td>
<td>NA/0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel + beva 15 mg/kg</td>
<td>365</td>
<td>NA/14.8</td>
</tr>
</tbody>
</table>
## Incidence of hypertension in selected phase III trial of VEGFR TKIs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th>Regimen</th>
<th>Patient, n</th>
<th>Hypertension, % All grade/ Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>Demetri et al</td>
<td>placebo</td>
<td>105/207</td>
<td>4/11/0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunitinib, 50 mg/d (4w on, 2w off)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRCC</td>
<td>Motzer et al</td>
<td>INFα</td>
<td>360/375</td>
<td>1/24/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunitinib, 50 mg/d (4w on, 2w off)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escudier et al</td>
<td>Placebo</td>
<td>452/451</td>
<td>2/17/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib, 400 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mHCC</td>
<td>Llovet et al</td>
<td>Placebo</td>
<td>297/302</td>
<td>2/5/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib, 400 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chen et al</td>
<td>Placebo</td>
<td>75/149</td>
<td>1.3/18.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib, 400 mg twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mCRC</td>
<td>Hecht et al</td>
<td>Placebo + FOLFOX</td>
<td>583/585</td>
<td>NA/NA</td>
</tr>
<tr>
<td></td>
<td>Kohne et al</td>
<td>Vatalanib + FOLFOX</td>
<td>855</td>
<td>NA/NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + FOLFOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vatalanib + FOLFOX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Relative risk of hypertension induced by antiangiogenic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypertension incidence [IC, 95%]</th>
<th>Relative risk [IC, 95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (≥10mg/kg)</td>
<td>25.4% (21.3 - 30.1%)</td>
<td>7.5 (4.2 - 13.4%)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>22.5% (19.5 - 25.9%)</td>
<td>3.9 (2.6 - 5.9%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>23.4% (16.0 - 32.9%)</td>
<td>6.1 (2.4 - 15.3%)</td>
</tr>
<tr>
<td>Axitinib</td>
<td>61.0%</td>
<td>Unknown</td>
</tr>
<tr>
<td>VEGF Trap</td>
<td>31.6%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Zhu et al. Lancet Oncology, Volume 9, 2;2008:117-123
Hypertension as a result of angiogenic inhibitors

- **Frequent adverse events**
  - Incidence: 22.5% to 57.7%
  - moderate intensity (< grade 3) in the majority of patients
  - controllable in most patients with standard antihypertensive therapy

- **Occur with drug initiation, usually after several weeks of treatment**

- **Dose dependent effect**
  - higher rate of hypertension with more potent VEGFRs TKI such as cediranib or axitinib
  - VEGF inhibition by bevacizumab
    - phase II in renal cell cancer (RCC): 36% of hypertension in high dose group as compare to 3% in low dose group
    - phase III in NSCLC (Avail trial): 9% of hypertension ≥ grade 3 in high dose group as compare to 6% in the low dose group

Risk factors of hypertension occurrence upon angiogenic inhibitor

- Pre-existing risk factors for hypertension
  - Older age
  - Overweight or obesity
  - Unhealthy Lifestyle Habits: eating sodium, drinking alcohol, smoking, not enough physical activity

- Pre-existing hypertension

- Metastatic RCC cancer

- Alternatively: certain VEGF polymorphisms might be associated with lower risk of grade 3 or 4 hypertension
Monitoring of blood pressure in patients treated with angiogenic inhibitors

- Different types of monitoring for BP have been proposed in the literature:
  - 3 ambulatory measures (the mean of three morning measurements at 5-min interval, also three night measurements for 3 days/week)
  - weekly during the first 6 weeks of treatment

- thereafter HTN should be monitored and treated according to the standard medical practice.

Wu et al, Lancet Oncol 2008; 9:117-123
Azizi et al. NEJM 2008;358(1):95-a-97-a
Management of hypertension

• Rule out kidney toxicity of antiangiogenic agents
  • Calculation of creatinine clearance
  • Glomerular lesion: proteinuria
  • Renal thrombotic microangiopathy: search for marker of hemolytic anemia or thrombocytopenia

• Hypertension should be managed as in patient without cancer
  • Patient w/o comorbidities: target blood pressure (BP) < 140/90 mmHg
  • Chronic kidney disease: target BP < 135/85 mmHg
  • Proteinuria: drugs inhibiting renin-angiotensin system

• Antiangiogenic agent should be continued without dose reduction unless severe or persistent hypertension is present

Which antihypertensive drug should be used?

- Lack of controlled studies addressing this question

- Various classes of antihypertensive drugs may be used
  - if proteinuria: Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin 2 receptor antagonist (ARA) may be considered
  - calcium channel blockers (CCB)
    - non dihydropyridine (verapamil, diltiazem) should be avoided because of CYP3A4metabolism
  - increase NO: Nitrates, phosphodiesterase inhibitors, nebivolol
Antihypertensive agents and angiogenic inhibitors: Caution

ACEI, ARA, diuretic, beta-blockers, alpha-blockers, nitrate derivates, calcium channel blockers

Low interaction potential

Nifedipine, calcium channel blockers

Use cautiously

Verapamil*
Diltiazem*
Inhibit CYP3A4

Contraindicated with Al

*Verapamil and diltiazem may not be used in combination with oral angiogenesis inhibitors due to CYP3A4 inhibition but may be used with bevacizumab and VEGF-trap
Prospective investigation of hypertension management during administration of cediranib (VEGFR TKI)

- Patients (n = 126) with advanced solid tumors were randomly assigned to one of four groups:
  - cediranib 30 or 45 mg/d +/- antihypertensive prophylaxis
  - prophylaxis: Calcium Channel Blocker (CCB) 3-7d before cediranib start

- Median time to onset of severe hypertension: 7 days, within the first 15 days of treatment for 14/19 patients

<table>
<thead>
<tr>
<th></th>
<th>CCB prophylaxis</th>
<th>No prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypertension</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Cediranib discontinuation due to AE</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>
Management of hypertension before initiation of angiogenic inhibitors (AI)

BP Measurement at baseline

Nal BP < 120/80
Pre HT 120<SBP<140 80<DBP<90
Stage 1 HT 140<SBP<160 90<DBP<100
Stage 2 HT SBP>160 DBP>100
Cardiovascular risk factor?
- Start AI drugs
- BP monitoring
+ Start CCB 3 to 7 days before introducing AI agent

BP monitoring under angiogenic inhibitor
- every week for the first 8 weeks
- before any infusion or cycle

Management of hypertension during angiogenic inhibitors (AI) therapy

BP monitoring under angiogenic inhibitor
- every week for the first 8 weeks
- before any infusion or cycle

BP<130/80
Continue AI agents

BP≥140/90
Hypertensive crisis
Stop AI agents
Hypotensive drugs

Medical history of ischemic cardiopathy

Yes
One test of 5 to 10 mg Isosorbide Dinitrate
Prompt BP normalisation
Reinforce previous anti HT treatment. Continue AI agents

No
Reinforce anti HT Medications
Continue AI agents

Add long acting nitrate derivates to previous anti HT treatment

Summary of recommendations

- Before starting AI therapy
  - preexisting kidney disease?
  - screening BP

- During therapy: BP assessment every week for the first eight weeks and before any cycle

- HTN definition level should be adapted according to JNC7 recommendations

- Elevated BP under angiogenic inhibitors
  - Angiogenic inhibitors withheld only if hypertensive crisis.
  - ACE inhibitors or ARA: patients with proteinuria, chronic kidney disease risks, or metabolic syndrome;
  - Dihydropyridine CCB in others patients
Conclusion

- Relationship between angiogenic inhibitors and BP has now been established

- Clinicians must recognize that angiogenic inhibitors used to treat cancer may exacerbate cardiac risk factors

- Proactive introduction or even prophylactic use of antihypertensive drugs can allow maintenance of therapy despite the onset of HTN.

- Clinicians should address issues related to the reduction of HTN risk factors, in addition to managing the patient’s cancer disease.
THANK YOU!

E-Module released in December 2009