ANTI-ANGIOGENIC AGENTS

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Talk Topics

- Introduction.
- Proposed MOA for Anti-Angiogenic Agents (AAA).
- Classes and examples of AAA.
- Focusing on Bevacizumab.
- Toxicity of AAA.

Introduction

- Chemotherapy (CTH) lacks specificity resulting in damage to both cancer and normal cells, creating a narrow therapeutic index. Trying to avoid the CTH side effects on normal cells, often suboptimal doses are being given, resulting in incomplete response, treatment failure, disease relapse, drug resistance, and metastatic disease.

- Growth of tumor cells is dependent on their capacity to induce angiogenesis (new blood vessels formation) to supply them with oxygen and nutrients (generally, tumor can not grow beyond 1-2 cubic mm without angiogenesis). So, It's been postulated that developing agents that can specifically target these new blood vessels would result in decent benefit rates with minimal, if any, side effects.

Introduction

- Tumor blood vessels are distinct from normal resting blood vessels; the former have perivascular detachment, vessel dilatation, and irregular shape. It's believed that they are not smooth like normal blood vessels, and are not ordered sufficiently to supply oxygen and nutrients to all tissues.

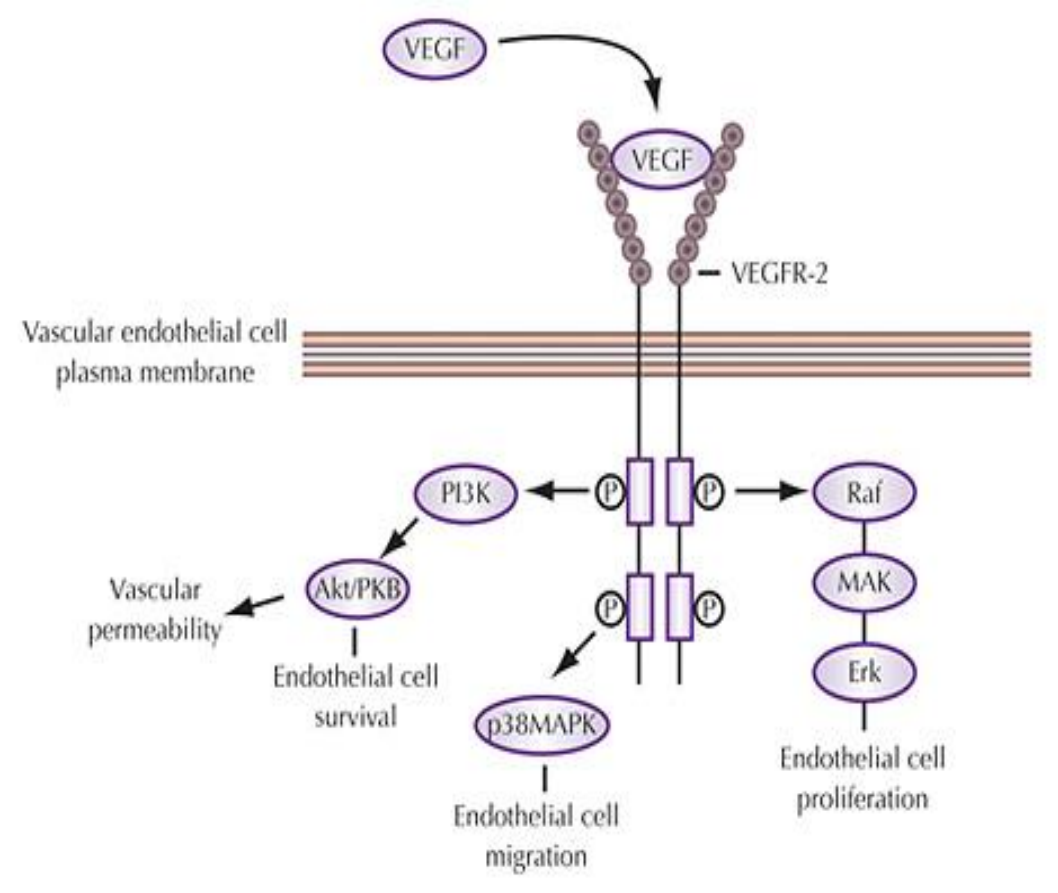
- Evidence now suggest that the tumor new blood vessels are in fact, mosaic vessels; composed of both endothelial and tumor cells. This mosaicity allows for shedding of tumor cells into the vasculature, possibly contributing to the appearance of CTCs in the peripheral blood

Introduction

VEGF is crucial for tumor growth by promoting angiogenesis.

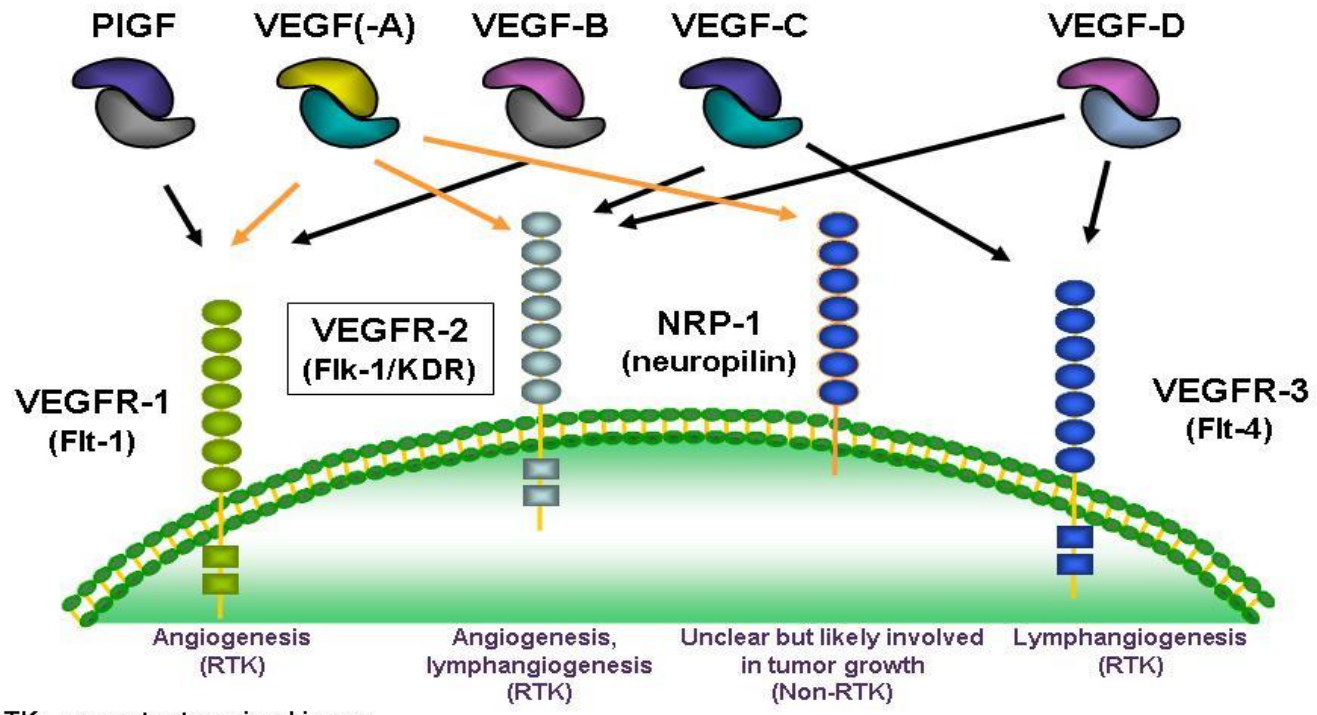
VEGF promotes:

1. Vascular permeability.
2. Endothelial cell survival, proliferation, and migration.



Introduction

The VEGF Family and Its Receptors

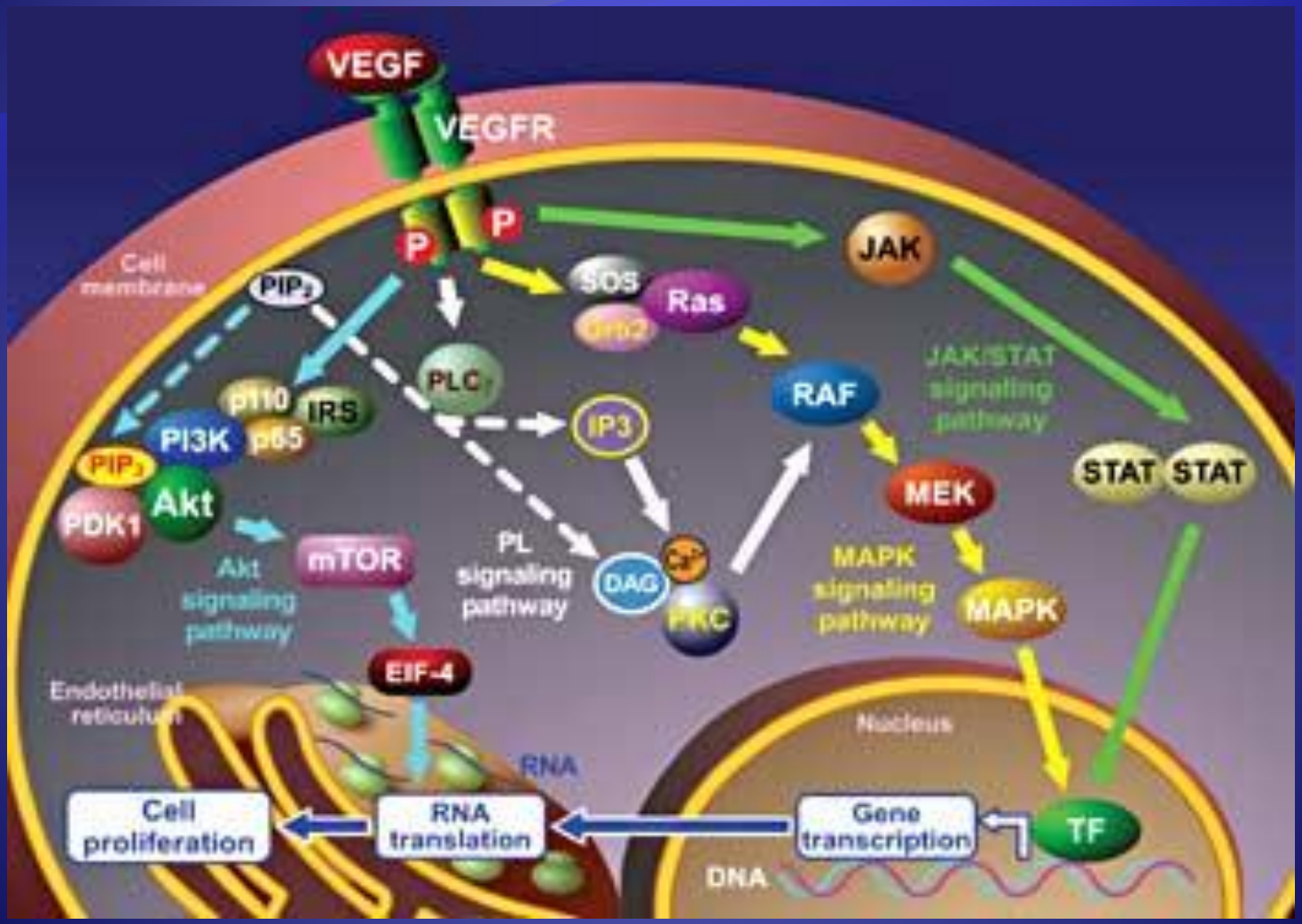


RTK = receptor tyrosine kinase.

Dvorak. *J Clin Oncol*. 2002;20:4368; Ferrara et al. *Nat Med*. 2003;9:669.

AVASTIN (bevacizumab)

Introduction



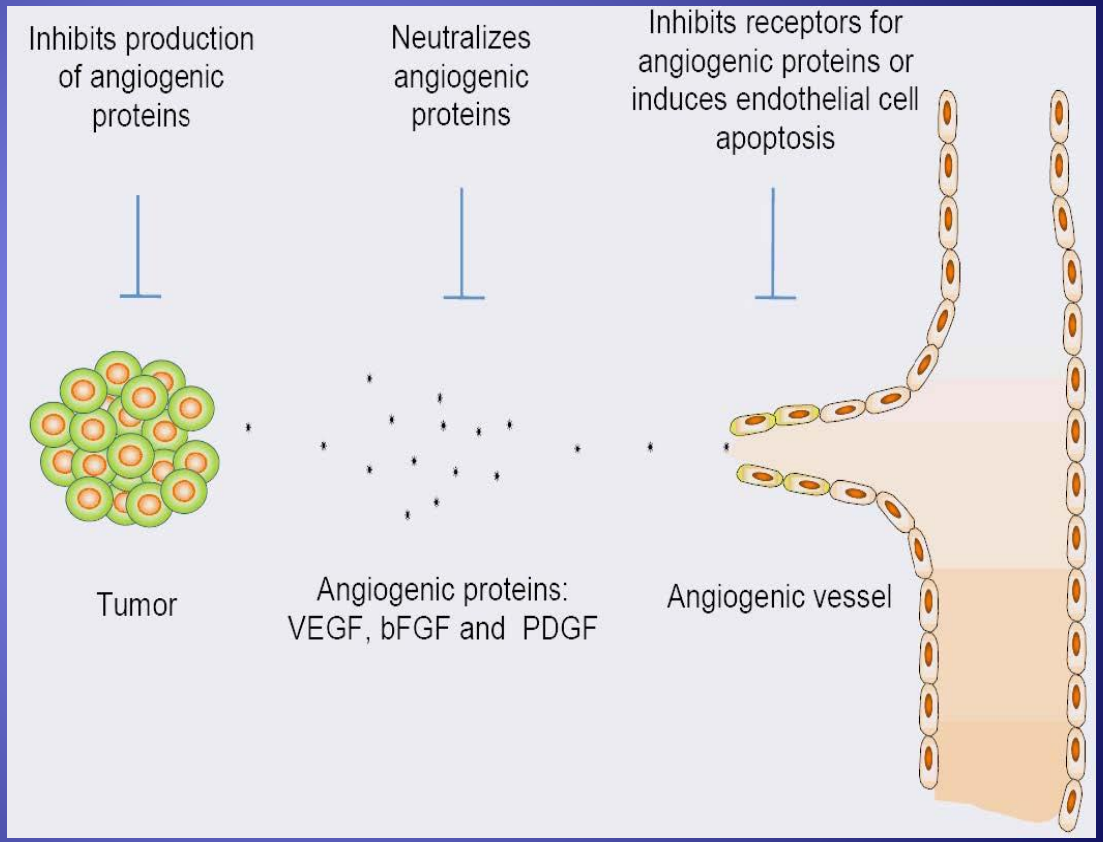
Introduction

- Anti-angiogenesis can be achieved through either:
  - **Chemotherapy:** the anti-angiogenic effect of CTH can be optimized by administering comparatively low drug doses on a continuous schedule; what 's known as metronomic CTH .
  - **Ligand-targeted agents:** will make possible better specificity with limited toxicity, these include:
    - Monoclonal antibodies.
    - Small-molecule inhibitors.

Anti-Angiogenic Therapeutic Drugs

May act by:

1. inhibiting synthesis of angiogenic proteins by cancer cells
2. Neutralizing the angiogenic proteins.
3. Inhibiting the receptors of endothelia for angiogenic proteins.
4. Directly inducing endothelial cell apoptosis.



Antiangiogenic Agents

Small-molecule TKIs

Sunitinib
Sorafenib
Pazopanib
Axitinib
Regorafenib

Monoclonal ABs

Bevacizumab
Ziv-Afibercept
Ramucirumab

(A) Small-Molecule Inhibitors

- Several tyrosine kinase receptors play crucial roles in tumors angiogenesis, therefore, serve for reasonable targets. The critical tyrosine kinase targets that have attracted the most interest are VEGFR, FGFR, and PDGFR. In the recent years, several small-molecule drugs have been approved.
- The **multi-target approach** has emerged as a new paradigm for the use of new kinase inhibitors (i.e. multi-targeted TKIs) , as:
  - more specific single target agents (e.g. Imatinib) may not have significant effects on cancer complexity.
  - Drug resistance is less likely to occur .
- Possible **mechanisms of drug resistance** include (as usual):
  1. Overexpression of key factors of signaling pathways.
  2. Drug-efflux system.
  3. Signaling bypass owing to mutations.

Small-molecule inhibitors

- Examples of currently approved multi-targeted TKIs:
  - **Sunitinib:**
    - selective inhibitor for VEGFR, PDGFR, Kit, Ret.
    - Clinical benefit: studies have demonstrated its definitive efficacy in advanced RCC, and in GIST refractory to imatinib.
  - **Sorafenib:**
    - Another selective oral multi-kinase inhibitor , it's broad activity against several tyrosine kinases including VEGFR and PDGFR.
    - Clinical benefit: approved for treatment of advanced HCC and advanced RCC.
  - **Pazopanib:**
    - Is a multi-targeted TKI against VEGFR-1, -2, and -3, PDGFR-α, PDGFR-β, and c-Kit.
    - Clinical benefit: approved for treatment of advanced RCC.
  - **Axitinib:**
    - A multi-targeted TKI against VEGFR-1, -2, and -3, PDGFR-α, PDGFR-β
    - Clinical benefit: approved for treatment of advanced RCC.
  - **Regorafenib:**
    - A multi-targeted TKI against VEGFR-1, -2, and -3, PDGFR-α, PDGFR-β, FGFR-1, FGFR-2, DDR-2, RAF-1, BRAF, ...
    - Clinical benefit: Recently approved for treatment of mCRC.

(B) Monoclonal Antibodies (MAbs)

- The use of MAbs is a promising approach to overcome difficulties in differentiating tumor cells from normal ones because they could be designed to selectively target tumor cells and trigger various responses.

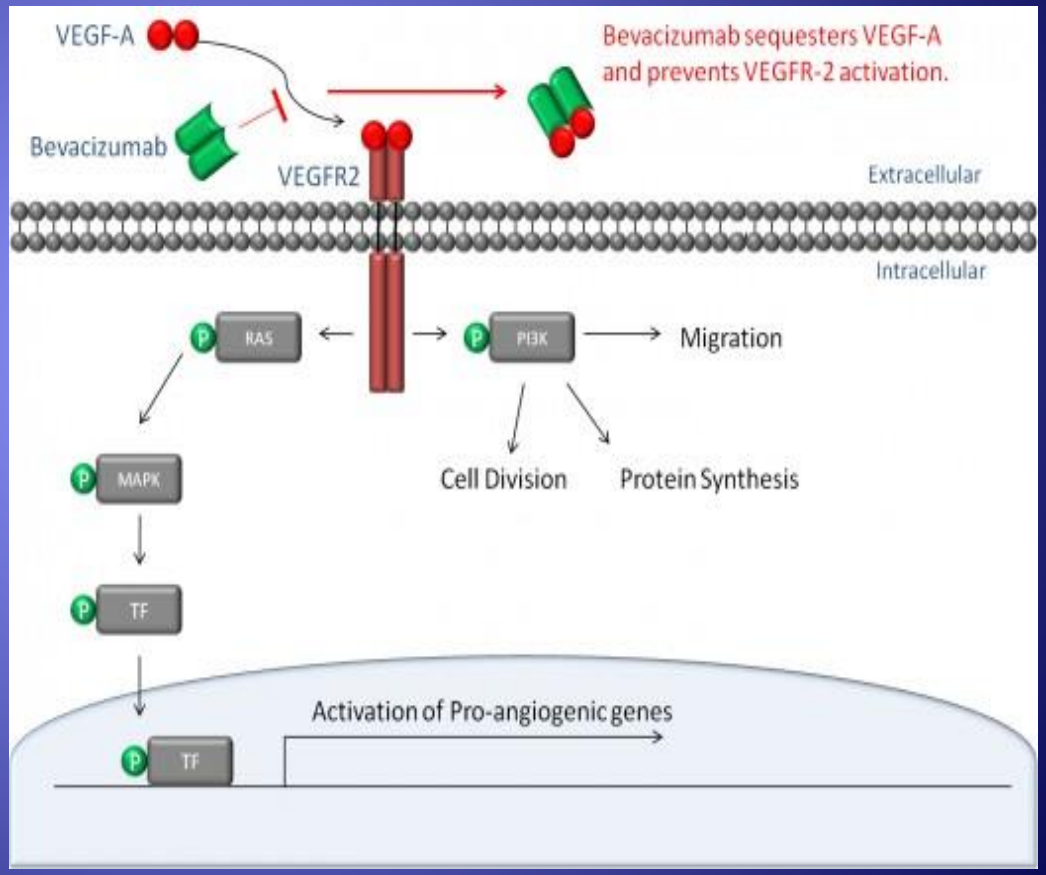
- These agents can act by: (generally speaking)
  - Directly kill cells by bearing toxic material.
  - Activating immune systems.
  - Blocking receptors.
- **Example**: Bevacizumab and Ramucirumab.

Bevacizumab (Bev)

It's a humanized MAb directed against VEGF, and considered to be a powerful angiogenic inhibitor.

Mechanism of action:

Bev. acts by sequestering VEGF-A resulting in the prevention of VGFR-2 activation, subsequently, this would inhibit pro-angiogenic genes , protein synthesis and cell division.



Indications

- **In 2004**: Bev. was ***FDA*** approved for the first time after a successful phase 3 trial for treatment of **mCRC** in the **1st-line setting**. The randomized double-blind clinical trial of > 800 patients clearly showed that the addition of Bev. To IFL chemotherapy improved ***mOS*** compared to IFL alone (**20.3** vs **15.5** respectively).

- **In 2006:** The ***FDA*** granted approval for a labelling extension for Bev. To be administered with FOLFOX4 chemo regimen in the **2nd-line treatment setting** of mCRC after progression on an Irinitecan-based therapy. This recommendation was based the results from the ***E3200*** trial which demonstrated a statistically significant improvement in mOS when Bev. Is added to FOLFOX4 vs. FOLFOX4 alone (13 vs 10.8 months respectively).

- **In 2006**: Bev. was granted ***FDA*** approval in combination with paclitaxel and carboplatin chemotherapies in the 1st-line setting of unresectable, locally advanced, recurrent, or metastatic **non-squamous NSCLC**. The approval was based on the ***E4599*** trial demonstrated a statistically significant improvement in ***mOS*** of adding Bev. to paclitaxel and carboplatin chemotherapy versus the same combination of chemotherapy alone (12.3 vs. 10.3 months respectively).

Bevacizumab ….. Indications

- **In 2008**: Bev. with paclitaxel combination was ***FDA*** approved in the 1st-line treatment of her2 –ve **locally recurrent or mBC.** The approval was based on results from the ***E2100*** study with nearly twice the ***mPFS*** compared to paclitaxel alone (11.3 vs. 5.8 months respectively).

- **In 2009**: Bev. was ***FDA*** approved as a single agent or combined with CTH (Irinotecan) in the treatment of **recurrent GBM** (2nd-line setting). The approval was based on demonstration of durable ***ORRs*** in two single-arm trials (***AVF3708g & NCI 06-C-0064E***).

- **In 2009**: ***FDA*** granted approval for the use of Bev. in combination with interferon alfa for the treatment of patients with clear cell with good or intermediate prognosis **mRCC**. This approval was based on the ***BO17705*** trial, which demonstrated a 5-months improvement in ***mPFS*** in patients treated with Bev.

- **In 2011**: FDA *revoked* Bev. indication for Her 2 –ve **mBC** (based on data showed increased cardiac toxicity (HF) that outweighed the clinical benefit obtained. However, the most recent NCCN guidelines (v3.2014) is still standing by Bev., and It's still being used for the same indication in Europe (still EMA approved).

Bevacizumab ….. Indications

- **In 2011:** Bev., together with standard chemo (Paclitaxel & Carboplatin), was approved by the European Commission (***EC***) in the EU for the treatment of **newly diagnosed Ovarian Cancer (OC).** The approval was based on data from 2 clinical trials *(GOG 0218 and ICON-7)*. In the *ICON-7* trial, the ***mPFS*** was extended in the Bev-Chemo group as compared to the chemo only group *(19.8 vs. 17.4* months), with a trend towards improved ***OS*** in the Bev. group which did not reach statistical significance which is why ***FDA*** approval for Bev. was not granted for this indication.

- **In 2012:** Bev. was approved in the EU in treatment of **recurrent platinum-sensitive OC**. The approval was based on the *OCEANS trial* which demonstrated statistically significant superiority of the Bev. Chemo arm (Gemcitabine/Carboplatin - GC) over the chemo only arm (GC) as regards: ***mPFS*** (*12.4 vs. 8.4* months respectively), ***ORR*** *(78.5 vs. 57.4% respectively)*, and duration of response (***DOR***) *(10.4 vs 7.4 months respectively).*

Bevacizumab ….. Indications

- **In 2014:** Bev. was again approved in the EU and by the ***NCCN*** panel in treating patients with **recurrent platinum-resistant OC**. The approval came after the results from the *AURELIA trial* in which Bev. combined with chemo (weekly paclitaxel, PLD, or topotecan) was compared to same chemo alone, the ***mPFS*** was almost doubled *(6.7 vs. 3.4* months) in the Bev. Chemo vs. chemo only arm respectively, ***ORR*** was *27.3 vs. 11.8%* respectively, and ***mOS*** was *16.6 vs. 13.3* months respectively, this ***OS*** survival trend was not statistically significant.

- **In 2014**: ***FDA*** approved Bev. in combination with paclitaxel and cisplatin or paclitaxel and topotecan as a treatment for patients with **persistent, recurrent, or metastatic cervical cancer**, based on the statistically significant extension of ***mOS*** in the phase III international randomized trial *GOG 240* . In this study the ***mOS*** for Bev. with chemo arm compared to chemo alone was *16.8* vs. *12.9* months respectively.

Bevacizumab ….. Indications To Sum Up

Indication	App. Auth.	App. Year	Trial/s	Design	Benefit
m**CRC** – 1st-line	***FDA***	2004	R - DB	Bev+IFL vs. IFL alone and	↑**mOS**
m**CRC**- 2nd-line	***FDA***	2006	E3200	Bev+FOLFOX4 vs. FOLFOX4 alone	↑**mOS**
Adv./Rec. Non-sq. **NSCLC**	***FDA***	2006	E4599	Bev+Paclit/Carbo vs. chemo alone	↑**mOS**
Rec. **BC** (loc/met)	***FDA***	2008	E2100	Bev+Paclit vs. Paclit. alone	↑**mPFS**
Rec. **GBM**	***FDA***	2009	AVG3708g & NCI06-C-0064E	Bev. Alone or + chemo (Irinotecan) vs. BSC or chemo alone	Durable ORR
m**RCC** (CC)	***FDA***	2009	BO17705	Bev+IFα vs IFα	↑**mPFS**
Rec. **BC** (loc/met)	***FDA revoke***	2011	----------	Bev. revoked	Still supp. By NCCN & EMA

Bevacizumab ….. Indications To Sum Up ….. continued

Indication	App. Auth.	App. Year	Trial/s	Design	Benefit
Newly Dx. **Ovarian Cancer**	***EMA***	2011	GOG 0218 & ICON-7	Bev+Paclit/Carbo. Vs. chemo alone	**↑mPFS**
Rec. Palatinum Sens. **Ovarian Cancer**	***EMA***	2012	OCEANS	Beb+Gem/Carbo vs GC alone	**↑mPFS, ORR, and DOR**
Rec. platinum Resist **Ovarian Cancer**	***EMA & NCCN***	2014	AURELIA	Bev+ w.Paclit, PLD, or Topo. vs. same CTH alone	**↑mPFS, ORR, & mOS**
Persist/Rec/Met. **Cervical Cancer**	***FDA***	2014	GOG 240	Bev+Paclit/Cis vs. chemo alone	**↑mOS**

Other AA Monoclonal ABs

Ziv-Aflibercept (ZALTRAP):

- recombinant fusion protein consisting of vascular endothelial growth factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1.

- **MOA:** It Inhibits angiogenesis by trapping VEGF-A, VEGF-B, and PLGF, factors.

- **Indication:** In 2012, *FDA* approved the use of ZALTRAP in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), for treatment of patients with **mCRC** that is resistant to or has progressed following an oxaliplatin-containing regimen, based on the results of the randomized double-blind multi-center ***VELOUR trial*** which demonstrated a statistically significant ***mOS*** extension when ZALTRAP was combined with FOLFIRI compared to FOLFIRI alone (*13 vs. 12* months respectively).

…. Other AA Monoclonal ABs

Ramucirumab (Cyramza):

- CYRAMZA is a human VEGFR2 antagonist.

- **Indication:** Treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent after failure of prior fluoropyrimidine- or platinum-containing chemotherapy.

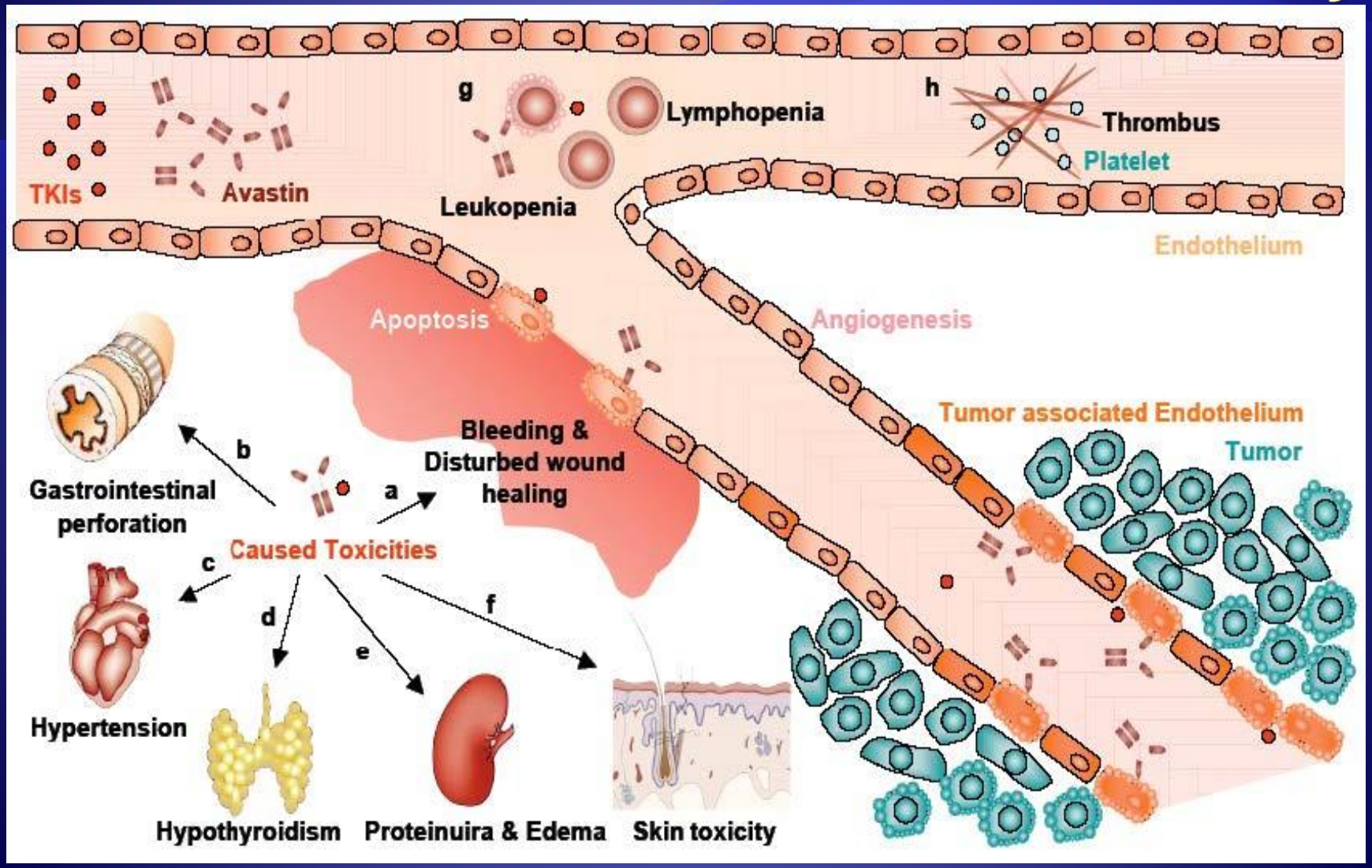
- **US Approval:** In 2014, It was *FDA* approved based on the *REGARD trial*, which showed a statistically significant improvement in ***mOS*** and ***mPFS*** when Ramucirumab was compared to placebo (*5.2 vs. 3.8 and 2.1 vs 1.3* respectively).

Toxicity

- It's been proposed that tumor-stimulated endothelial cells have a unique proliferating and migrating phenotype compared with the normal resting endothelial cells, and that targeting this phenotype would be so specific that no major side effects could occur, except for during wound healing and the menstrual cycle when most endothelial cells are more active.

- However, recent clinical experience has changed this expectation as:
  1. Angiogenesis is a very complicated multi-step biological process.
  2. VEGF plays an important role in other biologic effects including hematopoiesis, myelopoiesis, and normal endothelial cell survival.
  3. Multi-targeted TKIs: target multiple kinases of several different pathways, and so, toxicities in this case arises from concomitant inhibition of several other pathways.

Toxicity


TKIs
Avastin
g
Lymphopenia
Leukopenia
h
Thrombus
Platelet
Endothelium
Angiogenesis
Apoptosis
Tumor associated Endothelium
Tumor
Bleeding &
Disturbed wound
healing
b
a
Gastrointestinal
perforation
Caused Toxicities
c
d
e
f
Hypertension
Hypothyroidism
Proteinuira & Edema
Skin toxicity

Toxicity

- **Toxicities of angiogenic inhibitors include**:
  - **Bleeding, disturbed wound and ulcer healing, and GI perforations**:
    - Anti-angiogenic agents disturb the tight endothelial cell-platelet interaction with loss of vascular integrity.
    - Healing of GI ulcers also depends on angiogenesis.
    - VEGF is necessary for functioning of the intestinal villous capillaries.
  - **Thrombosis:**
    - Due to direct inhibition of normal endothelial cells which plays a major role in confining the coagulation reactions where the endothelium is intact.
    - VEGF is a survival and maintenance factor for the endothelial cell lining (sequestered by bevacizumab).
  - **Leukopenia, lymphopenia, and immunomodulation:** as VEGFRs are expressed by almost all hematopoietic cells and endothelial cell precursors, therefore, it's possible that inhibition of angiogenesis can cause not only leukopenia and lymphopenia, but also thrombocytopenia.

Toxicity

- **Hypertension and reduced LVEF:**
  - VEGF stimulates the endothelial cell to stimulate the production of nitric oxide synthase. Nitric oxide is used to relax the surrounding smooth muscles of blood vessels.
  - Anti-hypertensive drugs are quite effective in controlling bevacizumab induced increased BP, but sometimes the BP gets so high that it become life-threatening and cause damage to the eyes, brain, kidneys, and lungs.
  - Hypothyroidism and fatigue: this can be induced by the anti-angiogenic effect of TKIs on thyroid capillaries homeostasis.
- **Proteinuria and edema**: as renal function is partly regulated by VEGF, its inhibition causes mild proteinuria.
- **Skin toxicity:**
  - Growth factor signaling pathways are involved in the homeostasis of the skin, inhibition of angiogenesis can cause severe skin toxicity.
  - Examples: hair depigmentation, hair loss, and acral erythema are common during treatment with sunitinib and sorafenib.

THANK YOU

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