Targeted Oncologic Therapies and Abdominal Cancer Surveillance: Navigating and Anticipating the -ibs and -abs

Desmin Milner, MD¹, Kelly Godby, MD²,³ Jessica G. Zarzour, MD¹ Therese M. Weber, MD¹ Desiree E. Morgan MD¹,³

¹Department of Radiology
²Department of Hematology and Oncology
³Comprehensive Cancer Center
University of Alabama at Birmingham

No disclosures
Learning Objectives

1. Understand imaging consequences of effects of targeted oncologic agents on tumor biology
2. Become familiar with the more common types of targeted oncologic therapies, the molecular pathways activated or suppressed by the specific agents, and the correlative imaging responses

Target Audience: Radiology practitioners exposed to oncologic imaging and intimidated by diagrams like this...
Overview of classes of targeted therapies

Response assessment and consideration of why standard anatomic assessments fail

Response assessments that mirror targeted mechanisms

Specific case examples matched to mechanisms for assessment of response and complications
Targeted Agents

• As opposed to standard chemotherapeutic agents, targeted agents are drugs that affect specific pathways on cancer cells that regulate functions related to cell growth and cell death. Examples include:
  – Small molecule tyrosine kinase inhibitors
  – Monoclonal antibodies that block VEGF (vascular endothelial growth factor)
  – Immune response mediators

• Many of these drugs are cytostatic rather than cytotoxic
Targeted Therapy in a Nutshell

**Chemotherapeutic agents**: (cisplatin/paclitaxel, docetaxel/docetaxel + cisplatin)

**HDAC inhibitors**: LBH589

**Proteasome inhibitors**: Bortezomib

**Proteosome:** SUBSTRATE

**Cell cycle:**
- G1
- S
- M
- G2
- 17-AAG

**HDAC activators:** LBH589

**Proteasome inhibitors**: Bortezomib

**Blood vessel:** Bevacizumab

**Endothelial cell:** Bevacizumab

**Antibody-Drug Conjugate:** ASA404

**Tumor cell:**
- VEGF, bFGF
- HIF-1α
- ERK1/2
- p38MAPK
- p70 S6K
- AKT
- mTOR
- P13K
- RAS
- B-RAF
- MEK
- ALK
- PPI/Dasatinib
- Bevacizumab
- SU5402
- AZD2171
- Sunitinib
- Sorafenib
- ZD6474
- ASA404
- LBH589

**EGFR/HER-1/2/3**

**Src family kinases**

**GSK3 a/b**

**Jak inhibitors:** AG490

**AG1024 / PP1**

**ERK1/2 inhibitors:**
- PD184352
- U0126

**p38MAPK inhibitors:**
- SB203580
- SB202190

**STAT inhibitors:**
- AG490

**STAT1,2,3,5,6**

**STAT3 inhibitors:**
- AG490

**Jak inhibitors:**
- AG1024 / PP1

**STAT1,2,3,5,6**

**MEK inhibitors:**
- PD184352
- U0126

**RAS inhibitors:**
- BIBW 2992

**PDGFRα/β**

**PDGFRα/β inhibitors:**
- AZD2171
- Sunitinib
- Dasatinib
- Imatinib

**mTOR inhibitors:**
- BEZ235
- AZD2171
- Sunitinib
- Dasatinib
- Imatinib

**Cetuximab**

**HER-2 inhibitors:**
- Trastuzumab

**PDGFα/β**

**PDGFα/β inhibitors:**
- PDGF inhibitors

**ErbB3**

**ErbB3 inhibitors:**
- PF-0299804
- BIBW 2992

**c-Kit**

**c-Kit inhibitors:**
- Crizotinib
- PF-04217903

**PDGFRα/β inhibitors:**
- PDGFR inhibitors

**Bcr-Abl inhibitors:**
- Gleevec
- Imatinib
- Sprinib

**Statin inhibitors:**
- Atorvastatin

**Statin activators:**
- 18011

**ERK1/2 activators:**
- MEK1/2

**p38MAPK activators:**
- p38MAPK

**ERK1/2 activators:**
- MEK1/2

**p38MAPK activators:**
- p38MAPK

**ERK1/2 activators:**
- MEK1/2
Two Basic Principles to Remember:

- The “target”(s) are either found only on cancer cells, or are expressed to a greater degree on cancer cells than on normal cells.
- Traditional chemotherapy acts against ALL actively dividing cells, normal and malignant cells, causing side effects such as hair loss and GI effects.

  • Thus, targeted agents tend to be well tolerated by patients, with fewer side effects.
Guide to –ibs and -abs

-ib or -nib: small molecules that affect surface receptors or are able to pass into the cell to affect the cellular pathways

-ab or -mab: monoclonal antibodies that attach to the surface of cells to block undesirable pathways that promote cancer cell growth or trigger desirable pathways that promote cell death
An Example: Epidermal Growth Factor Receptor (EGFR)

Pleiotropic Effects of the EGFR on Tumor Growth and Metastasis

- Cell Motility and Metastasis
  - Cell adhesion, invasiveness

- Growth Effects
  - Proliferation, differentiation

- Angiogenesis Effects
  - Blood vessel recruitment, invasion, metastases

## Target Summary:

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR-HER2</td>
<td>Activates proliferation, angiogenesis, invasion, metastasis, and evasion of apoptosis</td>
</tr>
<tr>
<td>VEGF, PDGF</td>
<td>Activates malignant angiogenesis</td>
</tr>
<tr>
<td>PI3K/Akt/mTOR</td>
<td>Activates cancer cell growth and proliferation, evasion of apoptosis, synthesis of proteins necessary for cell growth, cell cycle progression, and cell metabolism</td>
</tr>
<tr>
<td>cKIT</td>
<td>Plays a critical role in cell proliferation and differentiation</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Cell growth and survival</td>
</tr>
<tr>
<td>Immune modulator</td>
<td>T cell mediated attack of tumor cells</td>
</tr>
</tbody>
</table>

Modified from RadioGraphics 2011; 31:2059–2091
Common Targets/Agents

- **Cell growth:**
  - HER-2: Human Epidermal Growth Factor Receptor 2 Protein - surface protein overexpressed on some cancer cells (example of agent: traztuzumab) BREAST, CERVIX, STOMACH/GE JUNCTION
  - BRAF: mutant form BRAF V600E on surface of melanoma cells (example: vemurafenib) MELANOMA
  - MEK: mitogen-activated protein kinase enzymes on BRAF- mutated melanoma and BRAF/KRAS mutated colon Ca (example: trametinib)

- **Signal transduction inhibitors:**
  - Imatinib, sorafenib, sunitinib, erlotinib, gefitinib, pazopanib

  GIST, HCC, RENAL CA, PANCREAS, LUNG, THYROID
**Common Targets/Agents**

- **Apoptosis inducers:**
  - Anti DR5 monoclonal antibodies (tigatuzumab)
  - Anti PD-L1 monoclonal antibodies

- **Angiogenesis inhibitors**
  - Anti VEGF monoclonal antibodies (bevacizumab)
  - Multikinase inhibitors (everolimus)

A full listing of targeted therapies approved by the FDA for specific cancer types and stages is available on the NCI website at: [http://cancer.gov/cancertopics/factsheet/Therapy/targeted](http://cancer.gov/cancertopics/factsheet/Therapy/targeted)
56 y.o. F with Gastro Intestinal Stromal Tumor (GIST): Responder to Imatinib (Gleevec)

PR through 7.17.13 with ↓ HU (Choi) and size (RECIST); PD 8.29.13 within larger inactive lesion
Imatinib:

• Specifically targets TK domain in abl (the Abelson proto-oncogene), c kit and PDGF-R (platelet-derived growth factor receptor) oncogenes

• In CML, the Philadelphia chromosome produces fusion of abl with bcr (breakpoint cluster region) → termed bcr-abl to create active tyrosine kinase therefore imatinib used to decrease bcr-abl activity

• Imatinib semicompetitively blocks phosphorlyation of tyrosine and activation of growth receptors, leading to cell apoptosis (cell death)
Imatinib:

- FDA approved for certain leukemias and blast crisis, Gastrointestinal Stromal Tumor, some dermatologic cancers
- Oral agent
- Side effects with imaging findings: none
- Related TKI inhibitors:

<table>
<thead>
<tr>
<th>Imatinib</th>
<th>Other drugs in same class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Everolimus</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
</tr>
<tr>
<td></td>
<td>Sunitinib maleate</td>
</tr>
<tr>
<td></td>
<td>Pazopanib hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Erlotinib Hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Lapatinib Ditosylate</td>
</tr>
</tbody>
</table>
CASE 2

53 y.o. M with Clear Cell Renal Cell Ca metastatic to the pancreas: Clinical benefit on pazopanib (stable disease x 30 mo); bowel Sx

No change in size during surveillance to date, although initial scan after commencing targeted therapy showed altered enhancement (bottom row)

TKI
Tyrosine kinase inhibitor targeting angiogenesis
Pazopanib:

- Multikinase inhibitor, affecting angiogenesis through c-KIT, FGFR, PDGFR and VEGFR enzyme alteration
- FDA approval for renal cell carcinomas, with recent Phase III trial showing similar objective response rates, median progression free survival (8 mo) and median overall survival (28 mo) compared to sunitinib, but better tolerated by patients
- Oral agent

CASE 3

58 y.o. F with Small Cell Lung Ca, progressive disease on topotecan (chemo) with pancreas metastasis: response to everolimus (mTOR inhibitor)

mTOR

Temporary clinical benefit on trial

3 months earlier

1 year later

26 months later
Everolimus:

- Specifically targets *Mammalian target of rapamycin*
- Works by blocking multiple mTOR pathways (see next slide) driving cell proliferative responses to external factors, blocks up-regulation of proteins affecting resistance to hypoxia
- FDA approval for pancreatic endocrine neoplasms, renal cell carcinomas, and hormone receptor-positive, HER2-negative breast cancer (the latter in combo with hormones-exemestane)
- Oral agent
mTOR pathway

50 y.o. F with Panc AdenoCa: Responder to Gemcitabine+ Nab-paclitaxel

Baseline 2 months 1 month
HU=78 HU=49 HU=34

PFS 13 months during clinical trial; by RECIST no PR, but mets clearly ↓ attenuation, and HU change more predictive of response

SPARC
Secreted protein, acidic, cysteine-rich (Osteonectin)

CASE 4
Morgan et al. RSNA 2011
SPARC: A matricellular protein that modulates cell-cell and cell-matrix interactions and may play a role in sensitizing therapy-resistant cancers.

- Highly expressed in the peri-tumoral stroma of many pancreatic tumors.
- May be important factor affecting drug accumulation and tumor response of albumin-bound drugs, including nab-paclitaxel (Abraxane) through albumin-SPARC interaction.
CASE 5

54 y.o. F with Her-2 neg, PR pos, ER neg breast Ca metastatic to the liver: Favorable response to anti-PDL1 monoclonal antibody

Marked change in size and number of new lesions 8 weeks after therapy initiation, center column NOT progressive disease but EXUBERANT immune response with subsequent confirmation on follow-up surveillance.
Anti PDL1 mAb

- **PDL1** = Programmed death ligand 1
  - Over expressed in tumor cells in order to escape immunosurveillance in the tumor microenvironment
- **PDL1** on normal dendritic cells typically binds programmed death 1 (PD-1) receptor on T cells and induces T cell apoptosis
- Blockade of interaction between PD-L1 on tumor cells and PD-1 on T cells reverses T cell suppression within tumors and promotes anti-tumor immune responses
- In clinical trials, not yet FDA approved

Semin in Oncol 2010; 37: 508-16
Anti-PDL1 mAb, immune modulator

Targeting immunosuppression by blocking the PD/L1 PD1 pathway
Side Effects

- Colitis associated with immune modulators (ipilimumab, others such as anti PD-L1)
- EGFR inhibitors (erlotinib, sorafenib, sunitinib, imatinib, etc, also colitis)
- Bowel perforation and pneumatosisis with multikinase inhibitors (sunitinib, sorafenib) and anti-angiogenic agents (bevacizumab)
- Fistula and GI bleeding (bevacizumab)

Ipilimumab - monoclonal antibody used for melanoma; inhibits cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) to induce the immune system to attack cancer cells, high risk for colitis, as in the above patient.
RESPONSE

- Since molecular targeted agents may be cytostatic or may induce apoptosis, clinical benefit is reflected in stable disease as well as partial response and complete response.
- RECIST (Response Evaluation in Solid Tumors) might not be ideal for all forms of targeted therapy.
- Choi criteria accepted for GIST.
- mRECIST and irRC for antiangiogenic and immune modulators—clinical trials now, in future your clinical practice.
RECIST 1.1

- Lesions at baseline must be measured in longest dimension with a minimum size of 10 mm
- Number of lesions required to assess tumor burden:
  - 5 total, 2 per organ
- Lymph node disease
  - Short axis dimension >15 mm
  - < 10 mm non-measurable
  - 10-15 mm non-target
- Progressive Disease
  - 20% increase in sum of the diameters
  - 5 mm absolute increase
  - New lesions
Choi Criteria

- Single longest dimension similar to RECIST
- Complete response: disappearance of all target lesions
- Partial response: 10% decrease in the size or decrease in tumor density (HU) of 15% or more on CT
- Stable disease: Insufficient shrinkage or growth to qualify for partial response/progressive disease
- Progressive disease: 10% increase in the size and does not meet criteria for partial response
  - New nodules within the tumor or increase in size of pre-existing tumor nodules
- Used predominantly for imatinib in GIST, novel application for sarcoma patients
irRC (simulating RECIST 1.1)

- May be based on target selection simulating RECIST 1.0 or RECIST 1.1
- New measurable lesions incorporated into tumor burden (>5 x 5 mm)
- New non measurable lesions do not define progression
- Non-index lesions contribute to defining irRC
- Progressive disease at least 25% increase in tumor burden in 2 consecutive observations at least 4 weeks apart
- Complete response: all index and new lesions gone
- Partial response: Sum of index and new lesions decrease > 50 %
- Stable disease: No change
- Progressive disease: Sum of index + new lesions increase > 25 %
- Used for immune modulators (ex: ipilimumab for melanoma)
References

• Tai IT, et al. SPARC in cancer biology: its role in cancer progression and potential for therapy. Drug Resist Updat 2008;11:231-246
• Tarhini A, et al. Phase II study of everolimus (RAD001) in previously treated small cell lung cancer. Clin Cancer Res;16(23);5900–5907

Thank you for viewing our poster!

dmorgan@uabmc.edu