Targeted Chemotherapy: Guiding patients to more personalized care

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Objectives

• Discuss the role targeted chemotherapy plays in the treatment of cancer patients

• Explore the decision making process used by practitioners to decide when to use targeted agents

• Outline several new targeted therapies that are currently being used in oncology practice
What is Targeted Therapy?

• Medications used to stop the growth, development or spread of cancer through the blockade of specific molecular targets around, on, or within the cancer cell
  – Most commonly include monoclonal antibodies (-mabs) and small molecule inhibitors (-nibs)
  – Often act only on a select number of cells
  – May be used alone or combined with traditional chemotherapy and/or radiation to enhance effects
Why Targeted Therapy?

- Allows for more personalized care
  - Reduces traditional side effects
  - Increases chance patient will see response

http://sitemaker.umich.edu/hbhe669final/personalized_medicine
Risks of Targeted Therapy

• Not all patients are candidates
  – Tumor may not express target
  – Tumor may have mutated to develop resistance to target interaction

• Unexpected adverse effects
  – “Off-target toxicities” include rash, metabolic effects, cardiotoxicity, etc.

• Risk of poor adherence

• High cost

Deciding to Use Targeted Therapy

• Art and Science
  – Observable facts
    • Symptoms
    • Diagnostic tests
  – Published data
    • Case reports
    • Clinical trials
  – Previous experience
    • Personal or collective

Deciding to Use Targeted Therapy

• Tumor diagnosis
  – Often certain targets are only seen in certain types of tumors
  – Ex: BCR-ABL and CML or CD20+ and DLBCL

• Receptor testing
  – Certain mutations/receptor variations may only be present in some tumors of a particular type
  – Ex: HER2 in breast cancer or ALK in NSCLC
Deciding to Use Targeted Therapy

• Mutation testing
  – Mutations may affect the ability of a patient to respond to a targeted therapy, even if they possess the desired target.
  – Ex: Cetuximab and CRC
Deciding to Use Targeted Therapy

• Receptor testing and mutation testing
  – Single point tests specifically looking for a particular receptor or mutation
    • Often developed along with a drug
    • Ex: BRAF testing in melanoma
  – Gene panels may be run to assess patients for a large number of mutations or receptor targets at once
    • Provides a more complete picture of an individual tumor
    • Ex: FoundationOne testing
Deciding to Use Targeted Therapy

• Clinical Trials
  – Turns hypothetical efficacy from laboratory observations into proven treatments
  – Communicates information between providers

• Guidelines
  – Helps to organize and stratify data from clinical trials
  – May include consensus opinion regarding clinical data
Specific Targeted Agents
Classes of Targeted Agents

• 2 major classes
  – Monoclonal Antibodies
    • Uses antigen-antibody relationship to bind very specific receptors
    • Bind outside of the cell to either directly turn off the receptor or deliver a chemotherapeutic drug directly to a cancer cell (conjugate monoclonal antibody)
  – Small Molecule Inhibitors
    • Small molecules that are able to enter cells in order to exert their effects on receptors
    • Work at many points along a cell signal pathway
Specific Targeted Agents

• Ado-trastuzumab (Kadcyla®, Breast)
• Pertuzumab (Perjeta®)
• Ibrutinib (Imbruvica®)
• Ramucirumab (Cyramza®)
• Nivolumab (Opdivo®)
Pertuzumab (Perjeta®)

• Monoclonal antibody
• Targets HER2 that is overexpressed in some breast cancers
  – Similar to trastuzumab, it prevents further signaling from HER2, limiting cell growth
  – Binds to a different location of HER2 than trastuzumab
    • Provides more complete HER2 block

Pertuzumab (Perjeta®)

- Deciding to use pertuzumab
  - Observable facts
    - Breast cancer with HER2 overexpression
  - Published data
    - Patients studied included those with metastatic breast cancer
      - Increased PFS ~6 months and OS by ~16 months
      - Only studied with trastuzumab and docetaxel
    - Also studied in those with locally advanced, inflammatory or early stage tumors (>2cm or N+) who have NOT received HER2 therapy
      - Increased pCR by ~17%
      - Studied with FEC, TCH and docetaxel neoadjuvant
    - Increased risk of cardiotoxicity
  - Previous experience
    - Recommended by NCCN as first line for metastatic breast cancer
      - May consider second line
      - More information is needed regarding ideal sequencing
    - May use with trastuzumab after AC for early disease

Ado-trastuzumab (Kadcyla®)

• Monoclonal antibody drug conjugate
• Targets HER2 that is overexpressed in some breast cancers
  – Differs from trastuzumab (Herceptin®) through the conjugate chemotherapy drug emtansine which is bound to the antibody
  – Antibody is internalized by cell to deliver chemo to cause cell destruction
Ado-trastuzumab (Kadcyla®)

• Deciding to use ado-trastuzumab
  – Observable facts
    • Breast cancer with HER2 overexpression
  – Published data
    • Patients studied had metastatic or recurrent disease
      – Increased PFS by ~3 months and OS by ~5 months
    • Found to cause cardiac and hepatotoxicity
  – Previous experience
    • Recommended by NCCN only after trastuzumab regimen
      – Preferred by NCCN for those with prior trastuzumab exposure
      – More information is needed regarding ideal sequencing
    • Recommended to stop therapy if no benefit or ECOG >3
Ibrutinib (Imbruvica®)

- Small molecule inhibitor
- Targets Bruton’s tyrosine kinase (Btk)
  - Enters the cell and binds to Btk to stop downstream signaling
- Btk is crucial to B-cell development
Ibrutinib (Imbruvica®)

• Deciding to use ibrutinib
  – Observable facts
    • Chronic lymphocytic leukemia
    • Mantle cell lymphoma
  – Published data
    • Mantle cell lymphoma patients had received at least 1 prior therapy
      – Found to have an overall response rate of 69%
    • CLL patients had received at least 1 prior therapy
      – Risk of progression was decreased by 78% and death was decreased by 57%
      – In those with high risk del 17p disease, the improved PFS was maintained
  – Previous experience
    • Well tolerated – recommended as category 1 for elderly/sick patients with CLL
    • First line agent for poor prognostic disease (17p deletion) CLL
    • Oral agent and expensive
    • Increased risk of bleeding
    • Increased drug interactions
Ramucirumab (Cyramza®)

- Monoclonal antibody
- Targets vascular-endothelial growth factor (VEGF2)
  - Similar to bevacizumab, but targets the receptor not the ligand
Ramucirumab (Cyramza®)

- Deciding to use ramucirumab
  - Observable facts
    - Metastatic non-small cell lung cancer (mNSCLC)
    - Metastatic colorectal cancer (mCRC)
    - Metastatic gastroesophageal (GE) junction or gastric tumors
  - Published data
    - mNSCLC
      - Studied in combination with docetaxel
      - Patients previously failed platinum based therapy; may have had bevacizumab
      - Improved OS and PFS by ~1.5 months
    - mCRC
      - Studied in combination with FOLFIRI
      - Patients previously failed therapy with 5FU, oxaliplatin and bevacizumab
      - Improved PFS by ~1.2 months and OS by ~1.5 months
    - Gastric/GE junction tumors
      - Studied as monotherapy or with paclitacel
      - Patients previously failed platinum or fluoropyrimidine regimen
      - Improved PFS by ~0.8-1.5 mo and OS by 1.5-2 months
  - Previous experience
    - Increased risk of bleeding and poor wound healing
    - Recommended as 2nd line agent in mCRC; bevacizumab is still preferred
    - Recommended as 2nd line agent in mNSCLC; no preference shown to other 2nd line agents
Nivolumab (Opdivo®)

- Monoclonal antibody
- Targets programmed death-ligand (PD-L1) receptors
  - These are upregulated in both melanoma and non-small cell lung cancers limiting the normal T-cell monitoring process that inhibits cell overgrowth

OPDIVO® (nivolumab) injection, for intravenous use. Bristol Myers Squibb. 3/2015
Nivolumab (Opdivo®)

• Deciding to use nivolumab
  – Observable facts
    • Metastatic non-small cell lung cancer (mNSCLC)
    • Progressive melanoma
  – Published data
    • Melanoma
      – Patients had to have failed ipilimumab and BRAF inhibitor (if eligible)
      – Achieved overall response rate of 32%
    • mNSCLC
      – Patients had to have failed at least one prior platinum-based therapy
      – Improved OS by 3.2 months
  – Previous experience
    • Recommended 2nd line agent; no preference given compared to other 2nd line therapies
Summary

• Targeted therapies are becoming a mainstay within the treatment of cancer
• Allows clinicians to choose therapies that are more specific to tumor cells
  – Improves response while limits adverse effects
• The decision to use targeted therapy depends on the tumor type, presence of the target, mutation status as well as recommendations from literature
  – Risk/benefit of individual patient effects is always taken into account
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