PHARMACOLOGIC THERAPY OF CANCER

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Disclosures

- Stock holdings in Genentech, Amgen
- Will discuss some non-FDA approved uses of cetuximab, panitumumab, erlotinib, and bevacizumab
- Participate in research trials funded in part by Genentech, Amgen, Biogen-Idec, and BMS
- Have no proprietary interest in any of the agents to be discussed
PURPOSE OF TODAY’S TALK

- Explain how pharmaceutical agents affect cancer cell growth
- Discuss the mechanism of action of agents including chemotherapy, combination chemotherapy, monoclonal antibodies (MABs) to EGFR and VEGF, and tyrosine kinase inhibitors (TKIs)
- Present data relating to the use of biologic agents with chemotherapy or XRT
THE PURPOSE OF A CANCER CELL – “And G-d said, ‘be fruitful and multiply’ ”

- Process proteins to improve the local and systemic environment for growth
- Replicate genetic material to reproduce new and improved cancer cells
- Improve vascular supply to seek new nutritional supplies for better growth and survival
- Reduce apoptosis or cancer cell death
CELL CYCLE PHASES

- **G1**: period after cell division for cells committed to continued proliferation
- **S**: DNA synthesis period
- **G2**: pre-mitotic rest period
- **M**: chromosome condensation and cell division
- **Go**: resting non-dividing diploid cells
Classes of Pharmacologic Antineoplastic Agents

- Alkylating agents
- Antimetabolites
- Natural products
- Biologic agents
CHEMO AND CELL PHASES

- **S phase specific agents:** antimetabolites
- **M phase specific agents:** vinca alkaloids, epipodophyllotoxins, taxanes
- **Non-phase specific agents:** alkylating agents
ALKYLATING AGENTS

- Inhibit cell function by forming covalent bonds with biologically important molecules
- Alkylation sites: DNA, RNA, protein
- More active in proliferating tumors but not cell cycle specific
- Associated with second malignancies
FIGURE 19.4-1. A schematic representation of cellular DNA showing bifunctional covalently bonded cross-links from an antitumor alkylating agent with one cross-link inhibiting the progress of DNA replication.
<table>
<thead>
<tr>
<th>Alkylating Agents</th>
</tr>
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<tbody>
<tr>
<td>nitrogen mustard</td>
</tr>
<tr>
<td>estramustine</td>
</tr>
<tr>
<td>mechlorethamine</td>
</tr>
<tr>
<td>thiotepa</td>
</tr>
<tr>
<td>nitrosoureas</td>
</tr>
<tr>
<td>dacarbazine</td>
</tr>
<tr>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>ifophosphamide</td>
</tr>
<tr>
<td>melphalan</td>
</tr>
<tr>
<td>busulfan</td>
</tr>
<tr>
<td>platinum salts</td>
</tr>
<tr>
<td>procarbazine</td>
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</tbody>
</table>
ANTIMETABOLITES

- Mechanism of action: structural analogues which compete for positions in DNA or RNA or inhibit key catalytic or regulatory enzymes involved in DNA and RNA synthesis
- S phase specific, most active in rapidly growing cells
- Do not increase the incidence of second tumors
**ANTIMETABOLITES**

- **Folate analogs:** methotrexate
- **Purine analogs:** fludarabine, 6-MP
- **Pyrimidine analogs:** cladribine, pentostatin
- **Adenosine analogs:** cytarabine, 5-FU
- **Substituted ureas:** hydroxyurea
NATURAL PRODUCTS

- Antibiotics: anthracyclines
- Epipodophyllotoxins: etoposide
- Microtubule agents: impair mitotic spindle activity; vincristine, taxanes
- Enzymes: asparaginase
MECHANISM OF ACTION OF ANTII-MITOTIC AGENTS

- Vinca alkaloids: block polymerization of microtubules and thereby impair mitotic spindle formation in M phase.
- Taxanes: promote microtubule assembly and stability, thereby preventing the function of the mitotic spindle.
SELECTING COMBINATION REGIMENS

1. Drugs must have primary activity
2. Non-overlapping toxicities
3. Utilize optimal dose and frequency
4. Frequency and intervals of administration need to be adjusted for toxicities and effectiveness
BIOLOGIC AGENTS

- **EGFR**: Epidermal growth factor receptor inhibits the tyrosine kinase system; *cetuximab, panitumumab*
- **VEGR**: Vascular endothelial growth receptor inhibits TKI via EGFR; *bevacizumab*
- **TKI small molecules**: *erlotinib, gefitinib*
ROLE OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

- Growth factor receptors on the surface of cancer cells
- Present in different concentrations on the surfaces of various malignancies
- Affect many aspects of cell function through the tyrosine kinase system
- EGFR is present on 80-100% of HNSCC
- Prognosis correlates with EGFR
Mechanisms of Activation of Normal TKs

MECHANISM OF EGFR FUNCTION

- Endogenous ligands, eg. EGF, PGF and TGF-a; bind to EGFR and cause dimerization of EGFR receptors
- The receptors are internalized and stimulate autophosphorylation
- This stimulates tyrosine kinase (TK) signaling pathways
- TK activity promotes cellular proliferation, inhibits apoptosis, promotes angiogenesis, and promotes metastatic growth
Properties

Cetuximab/IMC-C22

- IgG1 (chimerized antibody)
- Exclusive for EGFR and its heterodimers
- Prevents ligand binding to EGFR
- Binds to EGFR with high affinity ($K_d = 2.0 \times 10^{-10} \text{ M})$: 1 log higher than the natural ligand
- Inhibits receptor internalization
- Blocks receptor dimerization, autophosphorylation, tyrosine kinase function, and signal transduction
Acne-like Rash

*Cetuximab/IMC-C225*

The most common toxicity reported in clinical trials of Cetuximab/IMC-C225 is a self-limiting acne-like rash:

- Sterile, nonsuppurative
- Characterized as multiple pustular lesions located on the face, neck, and trunk
- Generally appears during the first 3 weeks of therapy
- Resolves spontaneously upon cessation of treatment without scarring (4-8 weeks)
- <2% of patients withdrew from study due to skin rash
- Correlated with response
PANITUMUMAB

- EGFR MAB similar to cetuximab
- More “humanized” rather than “chimeric,” so hopefully less toxicity
- Multi-institutional clinical trial underway using chemotherapy +/- panitumumab is open at GBMC
ADDING EGFR AGENTS TO CHEMO FOR HNSCC

Under active investigation by many groups using cetuximab and other agents

The ‘EXTREME” trial (Vermoken, ASCO, 2007) showed a potential benefit
EXTREME TRIAL
CHEMO +/- CETUXIMAB
Vermorken, ASCO 2007 abst 6091

- 442 patients with metastatic or recurrent HNSCC
- Platin-based + 5-FU +/- cetuximab
- Median survival:
  - Combined: 10.1 months
  - Chemo alone: 7.4 months
Anti-EGFR Approaches

- **MAbs**
- **TKIs**
- **Toxin conjugates**
- **Antisense**

Signal transduction

Cell death

Protein synthesis

Courtesy of José Baselga
ERLOTINIB AND CHEMO FOR HNSCC (Kim, ASCO 2007, abst 6013)

- 50 patients with recurrent or metastatic HNSCC
- Docetaxel + cisplatin + erlotinib
- Median overall survival: 11 months
- Overall response rate: 67%
- Disease control rate: 95%
- Toxicities: diarrhea, nausea, rash
DO TKIs HAVE A ROLE FOR HNSCC?

- Under active investigation by numerous groups and companies

- Conflicting results
THE PROBLEM OF CHEMO-XRT

- Chemo-XRT is the basis of organ preservation for locally advanced HNSCC
- Chemo-XRT is highly toxic
- Could a less toxic pharmaceutical such as an anti-EGFR or TKI be substituted in place of chemo, especially for frail or elderly patients?
- Bonner trial
COMBINING XRT AND EGFR BLOCKADE

- Radiation increases EGFR expression in cancer cells

- Blockade of EGFR signaling sensitizes cells to the effects of XRT

- Combined XRT and cetuximab is tolerated well
BONNER STUDY - 1

- Phase 3 study of XRT alone vs XRT + cetuximab
- XRT: daily, bid or concomitant boost
- Node dissection for some N2 and N3
- Cetuximab weekly
- No chemotherapy
- Primary endpoint: local control
- Secondary endpoints: OS, PFS, overall response rate, safety
424 patients to two arms

Balanced groups

Compliance was balanced

Cetuximab-XRT group did better
<table>
<thead>
<tr>
<th>Variable</th>
<th>XRT alone</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional control</td>
<td>14.9 mo</td>
<td>24.4 mo</td>
</tr>
<tr>
<td>Prog free surv</td>
<td>12.4 mo</td>
<td>17.1 mo</td>
</tr>
<tr>
<td>OS median</td>
<td>29.3 mo</td>
<td>49.0 mo</td>
</tr>
<tr>
<td>OS rate at 3 yrs</td>
<td>45%</td>
<td>55%</td>
</tr>
</tbody>
</table>

**Median duration of response by site**

<table>
<thead>
<tr>
<th>Site</th>
<th>XRT alone</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>23.0 mo</td>
<td>49 mo</td>
</tr>
<tr>
<td>Larynx</td>
<td>11.9 mo</td>
<td>12.9 mo</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>10.3 mo</td>
<td>12.5 mo</td>
</tr>
</tbody>
</table>
Toxicity similar in both groups
Dose reduction < 5%
Treatment delay 14%
No exacerbation of acute and delayed toxicities of XRT
Severe late toxicities were 20% in both groups
No benefit for adding cetuximab to XRT for larynx and hypopharynx SCC
J. FOLKMAN, 1971: CONCEPT OF ANTIANGIOGENIC THERAPY OF CANCER

• avascular microscopic tumors cannot grow beyond 1-2mm in diameter unless they induce new blood vessel capillaries

• the angiogenic switch is turned on by production / secretion of “TAF” by tumor cells

• tumor growth can be stopped / controlled by antiangiogenic therapy, e.g. anti-TAF therapy

• intent of therapy is not curative, but long term control (dormancy inducing therapy)
VEGF IN HNSCC

- Role remains undefined
- Preliminary trials suggest the use of VEGF blockers in HNSCC may be safe
- Efficacy will only be shown by randomized clinical trials
- ECOG is about to embark upon a trial using chemotherapy +/- bevacizumab for recurrent and metastatic HNSCC
CAUTIONARY NOTE

- VEGF pharmaceuticals have toxicities: proteinuria, HBP, uncontrolled bleeding, nose bleeds, wound dehiscence, prevention of healing, TE fistulae

- These therapies are very expensive for the demonstrable benefit seen.
Clinical research is essential to elucidate what is justifiable and feasible.

The medical community needs to actively investigate these diseases and the lay community and political community need to back these trials with great enthusiasm.
FUTURE DIRECTIONS

- Determine the role of VEGF agents
- Determine the interaction of EGFR and VEGF
- Determine if it is possible to reduce therapy to certain groups of patients (HPV positive) and intensify for other groups
- Develop a format to encourage the participation of patients, pharmaceutical companies, and insurance companies in clinical trial
CELL CYCLE

There are three types of daughter cells:

Non-dividing and terminally differentiated

Continually proliferating

Resting but recruitable for mitosis
Physiological appearance of the “angiogenic switch”

The “angiogenic switch” leads to neovascularization, as shown in a rat tumor model.

Images reproduced with permission from Judah Folkman.
Role of Epidermal Growth Factor Receptor (EGFR) in Human Cancer

- EGFR critically regulates tumor cell cycle progression, repair, and survival, and is involved in tumor metastasis
- Binding of specific ligands to EGFR (e.g., EGF, TGF-α) activates the receptor and triggers signal transduction cascades that affect cell proliferation
- Many human cancers express EGFR on the cell surface
Multiple Potential Mechanisms of Action

**Cetuximab/IMC-C225**

- Blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction
  - Prevents repair and survival of tumor cells damaged by the effects of chemotherapy and radiotherapy
  - Potentiates apoptosis
  - Inhibits cell cycle progression
  - Decreases production of angiogenic factors
  - Inhibits invasion/metastasis
  - Elicits ADCC response
Role of Epidermal Growth Factor Receptor (EGFR) in Human Cancer

- EGFR critically regulates tumor cell cycle progression, repair, and survival, and is involved in tumor metastasis.
- Binding of specific ligands to EGFR (e.g., EGF, TGF-\(\alpha\)) activates the receptor and triggers signal transduction cascades that affect cell proliferation.
- Many human cancers express EGFR on the cell surface.
Enhanced Antitumor Activity
Cetuximab/IMC-C225 and Radiation Therapy
A431 human epidermoid carcinoma

Inhibition of Cell Cycle Progression

**Cetuximab/IMC-C225**

- Gene transcription
- Cell-cycle progression

**Diagram:**
- Ras
- Raf
- Sos
- Grb2
- MEK
- MAPK

**Graph:**
- Relative cell number (%)
- Cetuximab/IMC-C225 (nM)
  - 0
  - 0.2
  - 2
  - 20
  - 200

**Bar Chart:**
- Relative cell number (%) decreases with increasing concentration of Cetuximab/IMC-C225.

*Courtesy of José Baselga*
Preclinical Conclusions

- EGFR plays a critical role in regulating tumor cell growth, repair and survival, angiogenesis, invasion, and metastasis.
- EGFR is expressed in a significant percentage of human tumors.
- EGFR is correlated with poor patient prognosis, decreased survival, and/or increased metastasis.
- Agents that block EGFR activity result in multiple antitumor mechanisms.
- EGFR blocking agents may lead to effective therapies for EGFR-positive cancers.
Multiple Potential Mechanisms of Action

Cetuximab/IMC-C225

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  - Prevents repair and survival of tumor cells damaged by the effects of chemotherapy and radiotherapy
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  - Inhibits cell cycle progression
  - Decreases production of angiogenic factors
  - Inhibits invasion/metastasis
  - Elicits ADCC response
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage of Tumors Expressing EGFR (range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>25-79%</td>
<td>Salomon (1995); Messa (1998)</td>
</tr>
<tr>
<td>Colorectal – Advanced stage</td>
<td></td>
<td>Goldstein (2001)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>80-100%</td>
<td>Salomon (1995); Grandis (1996)</td>
</tr>
<tr>
<td>Pancreatic Advanced Stage</td>
<td>30-95%</td>
<td>Salomon (1995); Uegaki (1997); Abbruzzese (2001)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>40-80%</td>
<td>Fujino (1996); Rusch (1997); Fontanini (1998)</td>
</tr>
<tr>
<td>Renal Carcinoma</td>
<td>50-90%</td>
<td>Salomon (1995); Yoshida (1997)</td>
</tr>
<tr>
<td>Breast</td>
<td>14-91%</td>
<td>Klijn (1992); Beckman (1996); Bucci (1997); Walker (1999)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>35-70%</td>
<td>Bartlett (1996); Fischer-Colbrie (1997)</td>
</tr>
<tr>
<td>Glioma</td>
<td>40-63%</td>
<td>Salomon (1995); Watanabe (1996); Rieske (1998)</td>
</tr>
<tr>
<td>Bladder</td>
<td>31-48%</td>
<td>Salomon (1995); Chow (1997)</td>
</tr>
</tbody>
</table>
Rationale for EGFR Blockade

- Expression of EGFR or its ligands can contribute to the malignant phenotype via an autocrine or paracrine mechanism.
- EGFR is expressed in a significant percentage of solid tumors.
- EGFR blocking agents may inhibit tumor growth.
THE PROBLEM OF COMBINED CHEMOTHERAPY AND XRT FOR HNSCC -1

- Toxicity may be unacceptable
- Patient selection is important
- Toxicity may be short term (mucositis) or long term (stenosis, xerostomia)
- HNSCC have increased number of activated EGFR
- EGFR is associated with poor outcome for HNSCC
The growth rate of cancer cells may be faster, the same rate or slower than non-cancer cells.
The death rate of cancer cells may be faster, the same rate or slower than non-cancer cells.
The balance of cancer cell growth and death rates determines the affect of the tumor.
1. For chemo responsive tumors, proper drug dosing strongly affects tumor responsiveness

2. Dose reductions are associated with reduced cure rates even while the rate of complete remissions may remain constant

3. Dose reduction of 20% can result in a 50% cure rate reduction

4. Doubling the dose may increase tumor cell kill by one log (10-fold increase)
Gompertzian Growth Pattern

- S shaped growth pattern indicating the growth rate of many tumors decreases as the tumor outgrows its blood supply.
- Small tumors grow more rapidly.
MECHANISMS OF DRUG RESISTANCE - 1

Cellular and biochemical mechanisms

1. decreased drug accumulation:
   decreased drug influx
   increased drug efflux
   altered intracellular trafficking

2. decreased drug activation

3. increased inactivation of drug or toxic intermediates
MECHANISM OF DRUG RESISTANCE - 2

4. increased repair of drug-induced damage to DNA, protein or membranes
5. drug targets altered (quantitative, qualitative)
6. altered cofactor or metabolite level
MECHANISM OF DRUG RESISTANCE - 3

7. altered gene expression:
   DNA mutation, amplification, or deletion

8. altered transcription, post-transcription
   processing or translation

9. altered stability of macromolecules
MECHANISMS OF DRUG RESISTANCE - 4

Mechanisms relevant in vivo
  Pharmacologic and anatomic drug barriers
    (tumor sanctuaries)
Host-drug interactions
  Increase drug inactivation by normal tissues
  Decreased drug activation by normal tissues
  Relative increase in drug sensitivity of normal tissues (toxicity)
Host-tumor interactions
Multi-drug Resistance:
Resistance to one drug may result in resistance to multiple agents within the same class of agents or even across different classes.
Genetically encoded resistance via a class of genes called MDR1 and MDR2/MDR3.
Poorly understood but secondary to an attempt to remove exogenous and endogenous metabolites from cells.
Strategies to overcome MDR: increase intensity, continuous infusions, use of inhibitors of the P-glycoprotein pump.
Topoisomerase II (Top II) helps prepare DNA for replication by uncoiling DNA and cleaving the strands.

Top II inhibitors such as doxorubicin and etoposide inhibit religation of DNA.
Frequently more effective than single agent therapy although single agent cisplatin for HNSCC may be an exception
All drugs must have efficacy
Allows higher dosages than single agents
Provides a broader range of coverage of potentially resistant cells by different mechanisms of action
Prevents or delays the development of resistant clones
Depends upon non-overlapping toxicities
May allow the use of newer agents with very different mechanisms of action such as MABs and TKIs
Enhanced Antitumor Activity: Cetuximab/IMC-C225 and Cytotoxic Therapy

- MAPK
- MEK
- Gene transcription
- Cell-cycle progression
- PI3-K
- PTEN
- AKT
- STAT
- G1S
- G2
- SOS
- SOS
- RAS
- RAF
- GRB2
- MEK
- MAPK

Chemotherapy

Survival/Apoptosis

Proliferation/Maturation

Angiogenesis

Metastasis

Radiation

Courtesy of José Baselga (modified)
CHEMOTHERAPY FOR HNSCC

- Cisplatin is the single most effective agent
- Other platinum salts such as carboplatin may be easier to use and somewhat less toxic but are not as effective
- Curative patients = cisplatin; palliation = carboplatin
- Taxanes are the second best agent: paclitaxel (Taxol) and docetaxel (Taxotere)
- Best combination: cisplatin + docetaxel + 5-FU
HOW COMBINATION CHEMO WORKS FOR HNSCC

- Cisplatin + docetaxel: alkylating agent + microtubule stabilizer
- Cisplatin + 5-FU: alkylating agent + antimetabolite
- TFP: alkylating agent + antimetabolite + microtubule stabilizer

These combinations may increase tumor kill but not increase total toxicity.

Adding biologic agents such as MABs and TKIs may increase efficacy without increasing toxicity.
EGFR Signal Transduction

Gene transcription
Cell-cycle progression

Proliferation/Maturation
Survival/Apoptosis
Angiogenesis
Metastasis

Courtesy of José Baselga
HOW PHARMOTHERAPY IS USED

1. Induction (neo-adjuvant): primary management for widely disseminated cancer or prior to primary surgery or XRT
2. Adjuvant: therapy after primary surgery or XRT
3. Concurrent: usually with XRT where surgery is not felt to be the optimal therapy
4. Direct instillation: eg. Bladder Rx instillation, ovarian peritoneal chemo
## Cetuximab/IMC-C225 and ZD1839

<table>
<thead>
<tr>
<th>Property</th>
<th>Cetuximab/IMC-C225</th>
<th>ZD1839</th>
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<tbody>
<tr>
<td>Specificity</td>
<td>Exclusive to EGFR</td>
<td>EGFR but variable</td>
</tr>
<tr>
<td>Target</td>
<td>External receptor</td>
<td>Tyrosine kinase</td>
</tr>
<tr>
<td>MOA/Activity</td>
<td>Interrupts cell cycle</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Induces apoptosis</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Anti-angiogenesis</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Downregulates MMP</td>
<td>N/A</td>
</tr>
<tr>
<td>Administration</td>
<td>I.V. weekly</td>
<td>P.O. daily</td>
</tr>
<tr>
<td>Dose Determination</td>
<td>Zero-order PK</td>
<td>MTD-diarrhea</td>
</tr>
<tr>
<td>Binding</td>
<td>Internalizes receptor</td>
<td>Reversible</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Acne-like rash</td>
<td>Acne-like rash</td>
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<tr>
<td></td>
<td>Grade 3/4</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>hypersensitivity (4%)</td>
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</table>
HISTORICAL PERSPECTIVE

- An explosion of a ship transporting mustard gas in Bari harbor during World War II resulted in lymphopenia amongst the sailors.
- The findings were evaluated by the Yale University Medical School.
- These findings resulted in the first use of chemotherapy in cancer patients.
- The findings were a closely held “military secret” which did not become known until the end of the war.
- Thus begins the era of modern chemotherapy.