The Role of Insulin-like Growth Factors in Cancer Therapy

Pharmacotherapy Grand Rounds
October 30, 2009

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Learning Objectives:
1. Describe the characteristics of the insulin-like growth factor (IGF) system
2. Explain preclinical rationale for targeting IGF system in cancer therapy
3. Outline the goals of phase I and phase II clinical trials targeting IGF receptor (IGF-1R) in malignancies
4. Discuss future potential of IGF-1R inhibitors in pharmacotherapy
I. Background

A. Cancer prevalence and epidemiology\textsuperscript{1}
   1. Total of 1,479,350 new cancer cases and 562,340 deaths from cancer are projected to occur in US this year
   2. By the year 2050, incidence and death rates are expected to double
   3. Cancer will affect at least 40% of the population in their lifetime
   4. Today, cancer accounts for more deaths than heart disease in those < 85 years old

B. Evolution of cancer\textsuperscript{2,3}
   1. Multistep process
      i. Neoplastic formation is non-lethal genetic damage to the cell
      ii. Tissue invasion, promotion and progression
   2. Various etiologies cause malignant transformation of the cell
      i. Chemical
      ii. Viral
      iii. Radiation
      iv. Genetic
   3. Various acquired capabilities allow tumor growth
      i. Self-sufficiency in growth signals
      ii. Evades apoptosis
      iii. Insensitivity to anti-growth signals
      iv. Sustained angiogenesis
      v. Potential to replicate
      vi. Tissue invasion and metastasis

C. Therapy modalities\textsuperscript{2}
   1. Surgery
      i. Primary role for local control of solid, slow growing tumors
      ii. First line defense in most cancers
   2. Radiation
      i. Ionizing source causes DNA strand breaks $\rightarrow$ prevents replication
      ii. First reported use in cancer was in the late 1800’s
         a. 60% patients will be treated with some type of radiation in their therapy course
   3. Chemotherapy
      i. Use of cytotoxic agents to attack tumors systemically
      ii. Conventional chemotherapy targets rapidly diving cells
      iii. Biologic therapy attempts to distinguish normal cells from cancer cells

D. Mechanism of resistance\textsuperscript{3}
   1. Cancer cells escape the toxic effect of commonly used cancer drugs
   2. Tumor related factors
      i. Poor absorption, inadequate doses and drug interactions
3. Intrinsic factors
   i. Drug activation
      a. Genes can produce chemo-inactivating proteins
   ii. Poor uptake
   iii. Increased drug catabolism
4. Acquired factors
   i. Increased efflux or decreased influx
      a. Mutated cancer cells can inactivate pump or mutate transporter (p-glycoprotein)
      b. Prevents drug or molecule from getting to the site of action
         1. Example: decreased expression of folate transporter for methotrexate activity
   ii. Repair mechanisms
      a. Malignant cells learn to repair damaged DNA
         1. Example: nucleoside excision repair with alkylating agents and platinum drugs
E. Overcoming resistance
   1. Novel mechanism of action
   2. Targeting growth pathways and signals (Figure 1)
      i. Advances have been made in the last decade to focus anti-cancer drugs on cellular signals
         a. Example: growth factor signal is widely implicated in oncogenesis
         b. Growth factors play a prominent role in the control of normal cellular processes in various tissues and organs
            1. Development
            2. Metabolic processes
            3. Physiologic processes
      ii. Disrupting cellular pathways and/or hormone activities can result in severe diseases
         1. Examples: diabetes, immune deficiencies, cardiovascular diseases, cancer, etc.
II. Growth Factors in Cancer

Figure 1. Cancer cell signaling

A. Insulin

1. Growth factor that exerts wide range of biological responses
   i. Glucose, lipid and protein metabolism
   ii. Cell proliferation and survival
2. Insulin binding results in rapid activation of the tyrosine kinase receptor
   i. Mediates tyrosine phosphorylation of a variety of endogenous substrates
      a. Increase level of growth factors (insulin-like growth factors)
      b. Increase cell sensitivity to growth factors necessary for cancer proliferation
3. Four observational studies reported various associations with insulin glargine and cancer incidence (Table 1)
4. July 2009 – FDA released early communication about the possible risk of cancer in patients using insulin
Table 1. Observational studies demonstrating use of exogenous insulin and increased cancer incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colhoun HM, et al. 2009⁵</td>
<td>Fixed cohort</td>
<td>Examine relationship with insulin glargine therapy in diabetic patients compared to other insulin analogues</td>
<td>No significant difference in non-glargine group compared to glargine only (HR = 1.02, p = 0.9)</td>
</tr>
<tr>
<td>Currie CJ, et al. 2009⁶</td>
<td>Retrospective cohort</td>
<td>Examine risk of solid tumor development in relation to oral hypoglycemic agents, human insulin and insulin analogues</td>
<td>Insulin based regimens had highest incidence of cancer (HR = 1.42, p &lt; 0.001)</td>
</tr>
<tr>
<td>Hemkens LF, et al. 2009⁷</td>
<td>Retrospective cohort</td>
<td>Evaluate risk of cancer and mortality in diabetic patients treated with human insulin or insulin analogues</td>
<td>Dose dependent increase in malignant neoplasms discovered with insulin glargine (p &lt; 0.001)</td>
</tr>
<tr>
<td>Jonasson JM, et al. 2009⁸</td>
<td>Prospective observational study</td>
<td>Evaluate the incidence of breast cancer, gastrointestinal cancer and prostate cancer with insulin glargine vs. other insulin analogues</td>
<td>Insulin glargine was associated with a significant increased risk of breast cancer only (RR = 1.99)</td>
</tr>
</tbody>
</table>

5. In vivo experimental studies demonstrate the growth and promoting effects of exogenous insulin⁹,¹⁰

6. Other prospective and observational studies have linked cancer to diabetes¹¹,¹²

B. Insulin’s role in cancer
   1. Target
      i. Under normal conditions, insulin functions specifically through a cell membrane insulin receptor
      ii. Experimental evidence suggests that increases in insulin leads to increases in insulin-like growth factor
      iii. In vitro studies reveal communication between insulin and insulin-like growth factors and their activation of similar receptors¹³

C. Insulin-like growth factor (IGF)⁴
   1. Role of IGF has been investigated for over 50 years
      i. Originally identified in 1957 as important mediator between growth hormone and childhood development¹⁴
   2. Epidemiological studies suggest associations between IGF and cancer (Table 2)

Table 2. Population studies demonstrating increased level of insulin growth factor and cancer risk

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Study</th>
<th>Population</th>
<th>Cancer Risk Related to IGF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Nurses Health Study¹⁵</td>
<td>397 cases/620 controls</td>
<td>Pre-menopausal 2.88 (1.21 – 6.85) Post-menopausal 0.89 (0.51 – 1.55)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Physicians’ Health Study¹⁶</td>
<td>193 cases/318 controls</td>
<td>2.51 (1.15 – 5.46)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Physicians’ Health Study¹⁷</td>
<td>530 cases/540 controls</td>
<td>Early-stage disease 1.2 (0.7 – 2.2) Late-stage disease 5.1 (2 – 13.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>MD Anderson¹⁸</td>
<td>204 cases/214 controls</td>
<td>2.06 (1.19 – 3.56)</td>
</tr>
</tbody>
</table>
3. IGF implicated in promoting oncogenic transformation, growth and survival of cancer cells
   i. Similar to insulin, IGF has characteristics of both circulating hormone and tissue growth factor
   ii. Most IGF’s are produced in liver and subject to hormonal/nutritional factors

III. IGF Pathway\(^{19}\) (refer to Figures 2 and 3)

![IGF Pathway Diagram]

Figure 2. Receptor ligand binding

A. Insulin-like growth factor 1 ligand (IGF-1)
   1. Growth hormone stimulates liver to produce and secrete IGF-1
      i. Also produced by kidney, lung and bone\(^{19,20}\)
   2. Under nutrition, growth hormone insensitivity, lack of growth hormone receptors or failure of downstream signaling pathway inhibits production
   3. Binds to specific IGF receptors
   4. Serves as a potent natural activator of the tyrosine kinase signaling pathway
      i. Stimulates cell growth and multiplication
      ii. Inhibits programmed cell death
   5. IGF-1 receptor (IGF-1R)
      i. May exist as homodimer or heterodimer
      ii. Both IGF-1 and IGF-2 binding sites
      iii. Transmembrane tyrosine kinase comprised of two extracellular ligand binding subunits

B. IGF-2 ligand\(^{20}\)
   1. Production is greatest in fetal tissue
      i. Other tissues secrete various amounts: brain, kidney, pancreas and muscle
2. Stimulates growth hormone during gestation
3. IGF-2 receptor (IGF-2R)
   i. Devoid of signal transduction capability
   ii. Binds only IGF-2

C. Insulin ligand
   1. Produced in the pancreas in response to various stimuli
   2. Insulin receptor (IR)
      i. Structurally related to IGF-1 receptor
      ii. At high concentrations, IGF-1 and IGF-2 activate both IGF-1R and IR

D. IGF signal transduction\textsuperscript{20,21} (refer to Figure 3)
   1. Relaying of a signal by conversion from one physical or chemical form to another
   2. Two pathways\textsuperscript{21} (refer to Figure 3)

\begin{center}
\textbf{Figure 3. IGF-1R activation and regulation}
\end{center}

3. PI3K $\rightarrow$ Akt $\rightarrow$ mTOR
   i. Phosphorylated insulin receptor subtype 1 (IRS-1) activates protein kinase B (Akt)
   ii. Akt enhances protein synthesis via the mammalian target of rapamycin (mTOR)
   iii. mTOR signals anti-apoptotic effects through phosphorylation and inactivation
4. Raf $\rightarrow$ MEK $\rightarrow$ ERK
   i. Recruitment of growth factor bound protein (Shc) and binding protein RAS $\rightarrow$ activation of a Raf protein kinase
   ii. Binding of Raf stimulates release of mitogen-activated protein kinase (MAPK)
   iii. MAPK activates extracellular signal related kinase (ERK) $\rightarrow$ release of nuclear factors resulting in cellular proliferation
5. IGF-1R stimulation
   i. Results in proliferation, survival and motility of cancer cells
   ii. IGF-1 plasma levels correlate with an increased risk for cancer
   iii. Activation of IGF-1R results in recruitment of multiple adaptor proteins and IGF-stimulated phenotypes

IV. Methods of Disrupting IGF Signaling$^{20-23}$
   A. Reduce IGF-1 levels
      1. Several reports demonstrate increased number of circulating IGF’s in various cancers (refer to Table 2)
   B. Neutralize IGF-1 and IGF-2
      1. IGF-1R is activated by binding of natural ligands
         i. Bind circulating ligand with soluble mutant IGF-1R
         ii. Inhibits the motility and metastasis of cancer cells
   C. Decrease expression of IGF-1R
      1. Antisense strategies
      2. RNA interference
   D. Inhibit IGF-1R activation (Figure 3)
      1. Inhibit tyrosine kinase activity by binding to ATP binding site or substrate binding side in the kinase domain of IGF-1R
      2. Create antibodies directed against IGF-1R

V. Clinical Development (see Table 3, Appendix A and Appendix B)
   A. IGF-1R antibodies
      1. First cloned receptor in 1986
         i. Limitations in early stages with concern over toxicity related to cross talk between IGF-1 and insulin
      2. Antibodies against the binding domain of IGF-1R
         i. Binding triggers receptor internalization and degradation with reduction in the receptor number on cell surface
      3. Examples:
         i. AMG 479 – fully humanized monoclonal antibody$^{24}$
            a. Binds IGF-1R with high affinity and inhibits ligand binding
            b. Does not block insulin from binding to the receptor
            c. Xenograft models – active in breast, pancreatic and colon cancer
ii. **CP-751,871** – fully humanized monoclonal antibody
   a. Inhibits IGF-1 binding to cells, inhibits IGF-1 induced phosphorylation → down regulation of IGF-1R expression at plasma membrane
   b. Only IgG2 subtype available

iii. **SCH 717454** – fully humanized monoclonal antibody
   a. Inhibits IGF ligand binding and IGF-stimulated receptor phosphorylation
   b. Inhibits IGF-1R downstream signaling and human tumor cell proliferation

B. Kinase inhibitors
   1. Small molecules that selectively inhibit tyrosine kinase domain of IGF-1R without significant effect on insulin receptor
   2. Potential to inhibit other kinases → expands activity of agent, but may increase toxicity
   3. Examples:
      i. **NVP-AEW541** - kinase inhibitor
      a. Induces apoptosis and cell cycle arrest in two colorectal cell lines

C. Antisense agents
   1. Use of approximately 20 nucleotides that bind to a target protein via hybridization
   2. Form a hybrid DNA-RNA duplex and prevent translation of a gene into a protein
   3. Examples
      i. **IGF-1R/AS ODN** – antisense agent
         a. Antisense oligodeoxynucleotide directed against IGF-IR

Table 3. New targeted agents for IGF receptors

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Structure</th>
<th>Trial Stage</th>
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</thead>
<tbody>
<tr>
<td>AMG 479</td>
<td>IGFR inhibitor</td>
<td>Phase II (breast, lymphoma, ovarian, pancreatic, sarcoma)</td>
</tr>
<tr>
<td>CP-721,871</td>
<td>IGFR inhibitor</td>
<td>Phase III (Non Small Cell Lung Cancer (NSCLC) Phase II (breast, colorectal, NSCLC, prostate, Ewing’s sarcoma)</td>
</tr>
<tr>
<td>IMC-A12</td>
<td>IGFR inhibitor</td>
<td>Phase II (breast, colorectal, head and neck, liver, pancreatic, prostate, sarcoma)</td>
</tr>
<tr>
<td>SCH 717454</td>
<td>IGFR inhibitor</td>
<td>Phase I</td>
</tr>
<tr>
<td>BIIB022</td>
<td>Kinase inhibitor</td>
<td>Phase I</td>
</tr>
<tr>
<td>R1507</td>
<td>Kinase inhibitor</td>
<td>Phase I</td>
</tr>
<tr>
<td>XL-228</td>
<td>Kinase inhibitor</td>
<td>Phase I</td>
</tr>
<tr>
<td>Nordihydroguareacetic acid</td>
<td>Kinase inhibitor</td>
<td>Phase I</td>
</tr>
<tr>
<td>IGF-1R/AS ODN</td>
<td>Antisense agent</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

IGFR = Insulin-like growth factor receptor
VI. Clinical Data
A. Differences in above mentioned new agents depends on pharmacological characteristics of each approach
B. Small molecular size may facilitate use at higher doses and in combination regimens
C. Given toxicity profile, monoclonal antibodies have reached the clinic much earlier compared to tyrosine kinase inhibitors
  1. Over 150 patients have been treated with IGF-1R antibodies to date
D. Published literature involves phase I and phase II clinical trials examining safety, pharmacokinetics and efficacy (refer to Table 4)

Table 4. Oncology nomenclature\textsuperscript{12-15}

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Phase I oncology trial</td>
<td>• Treatment of small cohorts of patients who failed standard therapy&lt;br&gt;• Goal to determine safety and maximum tolerated dose</td>
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<tr>
<td>Phase II oncology trial</td>
<td>• Treatment of hundreds of patients with disease to evaluate effectiveness for a particular indication&lt;br&gt;• Determines common short term side effects and response rates</td>
</tr>
<tr>
<td>Phase III oncology trial</td>
<td>• Determine therapeutic effectiveness/benefit ratio&lt;br&gt;• Primary endpoint is often survival, reduction in symptoms, or an endpoint that correlates with overall survival</td>
</tr>
<tr>
<td>Maximum tolerated dose (MTD)</td>
<td>Dose at which a given percentage of subjects experience toxicity</td>
</tr>
<tr>
<td>Dose limiting toxicity (DLT)</td>
<td>Predefined adverse events of grade 3 or 4 severity</td>
</tr>
<tr>
<td>Grading scale</td>
<td>National Cancer Institute Common Toxicity Criteria (NCI-CTC)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>Life threatening</td>
</tr>
<tr>
<td>Response evaluation criteria in solid tumors (RECIST)</td>
<td>Published rules that define when cancer patients improve (respond), stay the same (stable), or worsen (progress) during treatment</td>
</tr>
<tr>
<td>Anti-antibody formation</td>
<td>Screening for anti-drug immune responses as a requirement for regulatory and clinical outcomes</td>
</tr>
</tbody>
</table>
**Objective**

- **Primary:** determine safety, maximum tolerated dose (MTD) and pharmacokinetic (PK) parameters of AMG 479
- **Secondary:**
  - Examine pharmacodynamic (PD) parameters of tumor glucose metabolism
  - Evaluate human anti-AMG 479 antibody formation
  - Determine tumor response criteria (RECIST)

**Design**

- Phase I pharmacodynamic and pharmacokinetic study

**Population**

- Solid tumor patients who had progressed on conventional therapy

**Methods**

- Patients with advanced malignancies were treated with AMG 479 in escalating doses from 1 to 20 mg/kg IV

**Results**

- N = 16 with advanced malignancies treated with AMG 479
- Median number of cycles = 3 (range 1-16)
- Safety outcomes:
  - Grade 3 thrombocytopenia considered dose limiting toxicity (DLT) in 1 patient at 20 mg/kg
  - Grade 3-4 non-hematologic toxicities observed in 2 patients
  - No hyperglycemia greater than grade 2 occurred
  - Infusion reaction described in 1 patient at 20 mg/kg dose (Grade 2 chills/rigors)
- PK parameters:
  - Steady state reached following 3 doses
  - t ½ = 7-11 days
  - Mean clearance = 9-14 mL/kg/day
- Secondary outcomes:
  - Anti-AMG antibodies detected in 1 patient (no neutralizing antibodies)
  - RECIST criteria:
    - 1 patient with confirmed partial response (Ewing’s sarcoma)
    - 5 patients had stable disease
  - PET/CT scans
    - 1 breast cancer patient had a partial response

**Conclusions**

- AMG 479 appears to be well tolerated at doses up to 20 mg/kg dosed every 2 weeks
- AMG 479 administration results in PK values adequate for activity in preclinical models
  - Saturable binding of IGF-1R in neutrophils (receptor occupancy)
  - Preliminary anti-tumor activity

**Comments**

- Phase I trial demonstrates PK and PD data that will be applicable in phase II trials
- Early evidence of antitumor activity lends support for further research

Abbreviations: RECIST, response evaluation criteria in solid tumors; t ½, half-life; mL, milliliters; kg, kilograms; IV, intravenous

Objective
- Assess the safety, tolerability, pharmacokinetic (PK) profile and anti-tumor activity of AMG 479 in combination with either panitumumab or gemcitabine in patients with advanced solid tumors

Design
- Phase IB, open label, dose-escalation study

Population
- Inclusion: patients with advanced solid tumors, ECOG ≥ 2, no previous use of panitumumab or gemcitabine

Outcome
- Primary: incidence of adverse events; PK profile of AMG 479 in combination with panitumumab or gemcitabine
- Secondary: formation of anti-AMG 479 and anti-panitumumab antibodies, tumor response criteria
- Exploratory: levels of circulating IGF-1 and IGFBP-3

Methods
- 3 + 3 design
- Cohorts of 3 patients received AMG 479 at 6 mg/kg or 12 mg/kg IV every two weeks in combination with:
  - Panitumumab 6 mg/kg IV day 1, every 2 weeks
  - Gemcitabine 1000 mg/m² IV days 1, 8, and 15 of a 28 day cycle
- Assessments included dose-limiting toxicities (DLT) during the first 21 days and RECIST tumor response every 8 weeks

Results
- Total of 21 patients enrolled as of publication
- Median age = 57 years

<table>
<thead>
<tr>
<th>AMG 479 6 mg/kg</th>
<th>AMG 479 12 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Patients enrolled</td>
<td>6</td>
</tr>
<tr>
<td>Patients ongoing</td>
<td>0</td>
</tr>
<tr>
<td>Patients discontinued:</td>
<td>6</td>
</tr>
<tr>
<td>Disease progression</td>
<td>5</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>0</td>
</tr>
<tr>
<td>Adverse event</td>
<td>1</td>
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<tr>
<td>Consent withdrawn</td>
<td>0</td>
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</tbody>
</table>

- Safety analysis: 2 DLT’s in AMG 12 mg/kg cohort
  - Grade 3 hyperglycemia (patient removed from study per protocol)
  - Grade 4 neutropenia (in gemcitabine group)
- No treatment related deaths
- 14 patients tested positive for anti-AMG 479 antibodies
- Tumor response: RECIST criteria
  - Partial response in 73 yo male with metastatic, hormone-resistant prostate cancer
    - PR (58% by radiological assessment) after 16 weeks of therapy – still currently in trial
  - Partial response in 33 yo female with metastatic colorectal cancer
    - PR (54%) after 8 weeks of therapy, maintained PR for 9.4 months before progressing

Conclusions
- AMG 479 appears tolerable when combined with panitumumab or gemcitabine
- Demonstrates early anti-tumor activity in refractory disease
- Recommended phase II dose of AMG 479 in combination = 12 mg/kg

Comments
- Ongoing study, limited long term safety data available (published as abstract only)
- Data supports further investigation in phase II trials

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RECIST, response evaluation criteria in solid tumors; t ½, half-life; mL, milliliters; kg, kilograms; IV, intravenous

Objective
- Determine the safety and tolerability of CP-751,871 in patients with relapsed or refractory multiple myeloma

Design
- Phase I pharmacodynamic and pharmacokinetic study

Population
- Inclusion: >18 yo, life expectancy ≥ 3 months, ECOG ≤ 2, multiple myeloma (M spike ≥ 1g/dL, and/or serum free light chain ≥ 20 mg/L and/or urine M protein ≥ 200 mg/24 hours), adequate bone marrow function (ANC ≥ 1000/mm³ and platelets ≥ 75,000/mm³)
- Exclusion: prior stem cell transplant; myelosuppressive, immune, radiation, surgical or investigational therapy within 3 weeks; history of second cancer; concurrent significant medical disease; active bleeding; cardiac disease (including valvular dysfunction); symptomatic amyloidosis; cirrhosis; active pancreatitis; active uncontrolled infection; HIV, hepatitis B or hepatitis C

Outcome
- Primary: safety and tolerability
- Secondary: pharmacokinetic (PK) parameters, IGF-1R granulocyte expression, serum IGF-1 levels, antitumor activity

Methods
- CP-751,871 was administered IV on day 1 of 4-week treatment cycles at doses of 0.025 to 20 mg/kg in dose-doubling dose escalation cohorts of 3-6 patients
- Cohorts 1 – 9: CP-751,871 0.025 mg/kg – 6 mg/kg
- Cohort 10: CP-751,871 10 mg/kg
- Cohort 11: CP-751,871 20 mg/kg
- For each dose escalation, at least 3 patients had to complete cycle 1 without a dose limiting toxicity (DLT)
- At physician’s discretion, patients could receive salvage therapy: CP-751,871 with dexamethasone ± rapamycin

PK/PD
- All patients had PK levels taken 30 min before and 1 hr after infusion on days 1, 2, 3, 7, 14 and 21 of cycle 1
- Subsequent cycles – PK samples collected 30 min before and 1 hr after infusion, day 1 only
- Blood samples collected 30 min before and 48 and 72 hrs after infusion on days 2, 3, 4, 8, 15, and 22 of cycle 1
- Subsequent cycles – blood samples collected 30 min before infusion, day 1 only

Results
- 47 patients enrolled, received a total 252 treatment cycles, median 4 cycles per patient (range 1-17)

<table>
<thead>
<tr>
<th>Dose Cohort (mg/kg)</th>
<th># Patients</th>
<th># patients with CP-751,871 only</th>
<th># patients receiving dexamethasone</th>
<th># patients receiving rapamycin</th>
<th># cycles/cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>3</td>
<td>4</td>
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</tr>
<tr>
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<td>4</td>
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<td>5</td>
<td>3</td>
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</table>

- No CP-751,871 related events higher than grade 3 by NCI Criteria for adverse events (AE) were reported
- PK: t ½ at 20 mg/kg dose approximately 20 days
- Dose increases led to decrease in plasma clearance and increases in t ½ (potential saturation at higher doses)
- Only 1 DLT during cycle 1 was identified – grade 3 hyperglycemia (resolved with insulin)
- Efficacy: no objective responses were seen when CP-751,871 was given as a single agent
- 28 patients experienced disease stabilization, despite progression at study entry

Conclusions
- Phase II testing is warranted

Comments
- Combined modalities with dexamethasone and rapamycin is not typical for phase I trials

Abbreviations: HIV, human immunodeficiency virus; min, minute; hr, hour; t ½, half-life; mL, milliliters; kg, kilograms; IV, intravenous; NCI, National Cancer Institute

Background
- Addition of a third agent to platinum and taxane combinations may improve survival and decrease resistance in patients with non-small cell lung cancer (NSCLC)
- IGF-1R is often over-expressed in lung tumors and can mediate proliferation of lung cancer cells and resistance to conventional therapy

Objective
- Assess clinical efficacy of CP-751,871 in combination with paclitaxel (P) and carboplatin (C) in patients with previously untreated locally advanced or metastatic NSCLC

Design
- Multicenter, open-label, randomized non comparative phase II trial

Population
- Inclusion: >18 yo, confirmed stage IIIB or IV NSCLC, one measurable lesion according to RECIST, ECOG ≤ 1, ANC ≥ 1500/μL, platelets ≥ 100,000/μL, normal hepatic and renal function (as defined per protocol)
- Exclusion: childbearing potential declining contraception, active GI abnormalities, symptomatic brain metastasis, coexisting uncontrolled medical condition, radiation within 1 week, surgical procedure within 4 weeks

Outcome
- Objective response rate (ORR) = partial responses [PR]+ complete responses [CR]
  - PR = decrease by ≥ 30% tumor size
  - CR = disappearance of tumor

Methods
- Patients assigned 2:1 to receive paclitaxel 200 mg/m² IV and carboplatin AUC 6 every 3 weeks with (PCI) or without (PC) CP-751,871 at doses of 10 mg/kg (cohort 1) or 20 mg/kg (cohort 2)
- Eligible to receive up to 6 cycles of therapy or until disease progression or toxicity development
- Patients in PC arm that had progressive disease could cross over to CP-751,871 at investigators discretion

Statistical Analysis
- H₀ = 28% response in PCI arm (compared to 40% alternative response rate)
- 80% power with N=156

Results
- N= 156, with 151 evaluable; baseline characteristics between groups were similar
- Patients received a median of 4 cycles in both arms
- ORR (complete + partial response) = 54% in PCI arm (CI: 0.44 – 0.64) vs. 42% in PC arm (CI: 0.28 – 0.56) p < 0.001

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Not-identified</th>
<th>Adenocarcinoma</th>
<th>Squamous randomized</th>
<th>Squamous single arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (n=50)</td>
<td>53%</td>
<td>25%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>PCI 10mg/kg (n=48)</td>
<td>50%</td>
<td>38%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>PCI 20 mg/kg (n=53)</td>
<td>50%</td>
<td>57%</td>
<td>78%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Progression free survival (PFS) based on histology

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Not-identified</th>
<th>Adenocarcinoma</th>
<th>Squamous randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>69%</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>PCI 10mg/kg</td>
<td>50%</td>
<td>43%</td>
<td>67%</td>
</tr>
<tr>
<td>PCI 20 mg/kg</td>
<td>61%</td>
<td>69%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Safety:
- 8 deaths occurred (3 PC, 3 PCI10, 2 PCI20)
- Grade 3 and 4 hyperglycemia was observed in 8% PC and 15% PCI
- Other ADE’s = Grade 3 and 4 neutropenia, fatigue and thrombocytopenia were similar between groups

Conclusions
- PCI may constitute an efficacious and well tolerated therapy for locally advanced or metastatic NSCLC

Comments
- Limitations: phase II trial, small population, ORR primary endpoint
- Strengths: high response rates in squamous cell carcinoma, active control arm

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ANC, absolute neutrophil count; t ½, half-life; mL, milliliters; kg, kilograms; IV, intravenous
VII. Class Effects and Toxicity
   A. Endocrine - mild blood glucose elevations occurred in ~ 25% treated patients\textsuperscript{27-30}
      1. Increase gluconeogenesis, secondary to a loss of negative feedback at pituitary $\rightarrow$ elevations in circulating IGF-1, growth hormone and insulin
      2. Severe hyperglycemia is rare when given as single agent
      3. In combination with steroids, hyperglycemia occurred consistently in up to 20% of patients\textsuperscript{31}
      4. Cancer patients with diabetes were excluded from original trials
   B. Hematologic\textsuperscript{27}
      1. Thrombocytopenia considered dose limiting toxicity with AMG 479
      2. Grade 2-3 neutropenia observed with various IGF-1R inhibitors
   C. Hypersensitivity\textsuperscript{29,30}
      1. Rare occurring in < 10% treated patients

VIII. Future Directions
   A. Identify the role of IGF in cancer
      1. IGF-1R gene expression associated with various tumor suppressor genes and oncogenes\textsuperscript{32}
      2. Example:
         i. p53 tumor suppressor gene - protect cells against cancer
            a. Large number of human cancers exhibit mutations within p53 gene that impair tumor suppressor function
               1. Wild type p53 inhibits IGF-1R gene expression
               2. Mutant p53 upregulates IGF-1R gene expression
   B. Identify potential indications
      1. Major solid tumors
         i. Prostate, breast, colorectal and lung demonstrate IGF-1R activity
      2. Less common, aggressive tumors
         i. Myeloma patients demonstrate response with acceptable toxicity
         ii. Sarcoma patients demonstrate complete responses with monotherapy
   C. Derive reliable biomarkers predictive of response
   D. Identify patients with IGF-driven tumors
      1. Cross talk between IGF-1R and epidermal growth factor receptor (EGFR)
         i. Tumor cells that gain resistance to anti-EGFR have demonstrated upregulated IGF-1R
   E. Identify role in combination
      1. Antibodies, hormonal agents, insulin, oral hypoglycemic, etc.
IX. Summary

A. Insulin has been implicated in the role of carcinogenesis
   1. Targeting insulin and IGF-1 signaling is similar to other hormonal targets
   2. IGF-1R antibodies can control growth and development to regulate proliferation and survival

B. Epidemiological studies suggest IGF-1 and IGF-2 play a role in the promotion and growth of malignant cells

C. IGF system regulates metastasis
   1. Both IGF-1R and IR can serve as important targets in cancer therapy
   2. Targeting IGF-1R may be more difficult \(\Rightarrow\) IGF-1R is NOT amplified or mutated

D. Phase I trials examining targeted therapy at inhibiting IGF-1R demonstrate safety, tolerability and early response
   1. Adverse effects include glucose intolerance, anemia and mild thrombocytopenias

E. Phase II trials demonstrate that IGF-1R antagonists have early success in lung cancer

F. IGF-1R antagonists have promise as new cancer therapies
   1. Selectivity for agents that target this pathway are ongoing (phase III trials) and will hopefully validate this pathway as a therapeutic target
References


Appendix A. Summary of early clinical trials with insulin-like growth factor receptor inhibitors\textsuperscript{28-32}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Properties*</th>
<th>Biomarkers</th>
<th>Key Toxicities</th>
<th>Preliminary Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG-479</td>
<td>t $\frac{1}{2}$ = 7 – 11 days Dosed q 2 wks</td>
<td>IGF-1, IGF-1R, IGFBP-3</td>
<td>Thrombocytopenia, hyperglycemia</td>
<td>Phase I: complete response in Ewing’s Sarcoma, partial response in carcinoid tumor, partial response in colorectal cancer</td>
</tr>
<tr>
<td>AVE1642</td>
<td>t $\frac{1}{2}$ = 9 days Dosed q 3 wks</td>
<td>NA</td>
<td>Hyperglycemia, hypersensitivity</td>
<td>NA</td>
</tr>
<tr>
<td>Cixutumumab</td>
<td>t $\frac{1}{2}$ = 111 hrs Dosed q 2 wks</td>
<td>IGF-1, IGFBP-3</td>
<td>Hyperglycemia, anemia, psoriasis, infusion reaction</td>
<td>Phase I: stable disease for 9 months in 2 patients</td>
</tr>
<tr>
<td>CP-751,871</td>
<td>t $\frac{1}{2}$ = 20 days Dosed q 3-4 wks</td>
<td>IGF-1, IGF-1R, IGFBP-3</td>
<td>Hyperglycemia, anemia, arthralgia, fatigue, elevated LFTs</td>
<td>Phase I: complete response in Ewing’s Sarcoma, 9 partial responses in myeloma, 8 partial response in prostate cancer Phase II: 54% increased overall risk reduction in NSCLC</td>
</tr>
<tr>
<td>MK0646</td>
<td>t $\frac{1}{2}$ = 100 hrs Dosed q 1-2 wks</td>
<td>IGF-1R</td>
<td>Thrombocytopenia, gastrointestinal bleeding, pneumonitis, elevated LFTs</td>
<td>Phase I: stable disease for &gt; 12 months in 2 patients</td>
</tr>
<tr>
<td>R1507</td>
<td>t $\frac{1}{2}$ = 6 days Dosed q 1-3 wks</td>
<td>IGF-1R</td>
<td>Hyperglycemia, lymphopenia, cerebral vascular accident, bilirubin elevations</td>
<td>Phase I: 2 partial response in Ewing’s Sarcoma</td>
</tr>
<tr>
<td>SCH717454</td>
<td>t $\frac{1}{2}$ = 11 days Dosed q 2 wks</td>
<td>IGF-1R</td>
<td>Hyperglycemia</td>
<td>Phase I: stable disease &gt; 6 months in 7 patients</td>
</tr>
<tr>
<td>ZL228</td>
<td>t $\frac{1}{2}$ = 55 hrs Dosed q wk</td>
<td>IGF-1R, Insulin receptor</td>
<td>Syncope, hyperglycemia</td>
<td>Phase I: complete response in 2 CML patients, partial response in 2 ALL patients</td>
</tr>
</tbody>
</table>

Abbreviations: t $\frac{1}{2}$, half-life; hrs, hours; wks, weeks; IGF-IR, insulin-like growth factor receptor; IGFBP, insulin-like growth factor binding protein; NSCLC, non-small cell lung cancer; LFTs, liver function tests; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia.

*Estimated half-life and dosing schedule.
Appendix B. Summary of ongoing clinical programs with insulin-like growth factor receptor inhibitors^{30-32}

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and Combination</th>
</tr>
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<tbody>
<tr>
<td>Adrenocortical carcinoma</td>
<td>Mitotane (A12)</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>XL228</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Various anti-estrogens</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Single agent</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Single agent&lt;br&gt; In combination with:&lt;br&gt; • Cetuximab&lt;br&gt; • Cetuximab - irinotecan&lt;br&gt; • Panitumumab</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Single agent&lt;br&gt; In combination with sorafenib - erlotinib</td>
</tr>
<tr>
<td>Head and neck tumors</td>
<td>In combination with cetuximab</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>In combination with bortezomib</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Single agent&lt;br&gt; In combination with octreotide</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>In combination with:&lt;br&gt; • Erlotinib&lt;br&gt; • Paclitaxel - carboplatin&lt;br&gt; • Pemetrexed - cisplatin</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Single agent&lt;br&gt; In combination with:&lt;br&gt; • Paclitaxel - carboplatin</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>In combination with:&lt;br&gt; • Erlotinib - gemcitabine&lt;br&gt; • Gemcitabine</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Single agent&lt;br&gt; In combination with:&lt;br&gt; • Anti-androgens&lt;br&gt; • Docetaxel - prednisone&lt;br&gt; • Mitoxantrone - prednisone</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Single agent&lt;br&gt; In combination with:&lt;br&gt; • Doxorubicin</td>
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