SIMPOSIO AIRO–AION
Attualità nel trattamento del paziente metastatico

Le nuove “targeted therapies” in oncologia medica

Paolo Marchetti
Targeted Therapies

- Do cell signaling pathways have a place in clinical practice?
Targeted Therapies: The Beginning

  - SRC was identified as the first proto-oncogene
- Tony Hunter (PNAS, 1977)
  - SRC was identified as a tyrosine kinase involved in cell signaling.
Anno Domini 2000
Ji Luo et al., Cell 2009

Evading apoptosis

Self-sufficiency in growth signal

Tissue invasion & metastasis

Insensitivity to anti-growth signals

Sustained angiogenesis

Survival/Proliferation in foreign environments

Limitless replicative potential
Cells communicate with one another and respond to their environment predominantly by means of chemical signaling molecules that bind extracellular receptors on the surface or diffuse into the cell to bind internal receptors.

This process stimulates a cascade of proteins that amplify signals and deliver them to intracellular destinations, where they mediate changes in cellular activity.

Tyrosine Kinases and Cancer

- As key regulators of proliferation and growth, more than 30 RTKs have been implicated in cancer, as have the 2 main signaling pathways that they regulate:
  - the mitogen-activated protein kinase (MAPK) pathway
  - the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway
Signal reception activates cascade

Jane Wang,
*The Science Creative Quarterly, 2003*
~15 Years Later – How Have We Done?
Have our predictions/assumptions proved correct?

- Mixed Reviews on Efficacy:
  - Some very exciting: major gains, transforming disease outcomes.
Chronic Myeloid Leukemia Overall Survival: Imatinib Mesylate vs. Interferon-α

GI Stromal Tumour: Recurrence Free Survival
Imatinib Mesylate vs. Placebo

~15 Years Later – How Have We Done? Have our predictions/assumptions proved correct?

- **Mixed Reviews on Efficacy:**
  - Some very exciting: major gains, transforming disease outcomes.
  - Some modest -- but still practice changing
Renal Cell Carcinoma: Overall Survival
Sunitinib vs. IFN alpha

Motzer R J et al. JCO 2009;27:3584-3590
Erlotinib NSCLC Results: Erlotinib vs. Placebo (NCIC CTG BR.21)

- Erlotinib: 6.7 m
- Placebo: 4.7 m

*HR 0.71, p < 0.0001
Adjuvant Trastuzumab in HER2 Positive Breast Cancer – Overall Survival

Perez E A et al. JCO 2011;29:3366-3373
BRAF

Constitutive activation is independent of extracellular factors and does not respond to biochemical signals that would normally regulate activity.

RAS–RAF pathway

Normal activation of RAS via extracellular factors at the inner cell membrane via RTK

Normal cell proliferation and survival

Oncogenic BRAF signaling

Constitutively Activated pathway and downstream activity

Oncogenic BRAF signaling arrested with BRAF inhibitors

Selective binding of oncogenic BRAF kinase by vemurafenib, blocks the Constitutively Activated pathway and downstream activity

Progression-free survival (February 01, 2012 cut-off) censored at crossover

![Graph showing progression-free survival for Dacarbazine (n=338) and Vemurafenib (n=337).](image)

**Hazard ratio 0.38**
(95% CI: 0.32–0.46)
Log-rank \( p < 0.001 \) (post-hoc)

**No. at risk**

<table>
<thead>
<tr>
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<th>Dacarbazine</th>
<th>Vemurafenib</th>
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<tr>
<td>0 months</td>
<td>338</td>
<td>337</td>
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<tr>
<td>6 months</td>
<td>100</td>
<td>269</td>
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<tr>
<td>12 months</td>
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Overall survival (February 01, 2012 cut-off) censored at crossover

Vemurafenib (n=337)
Median f/u 12.5 months

Dacarbazine (n=338)
Median f/u 9.5 months

Hazard ratio 0.70 (95% CI: 0.57–0.87) p<0.001 (post-hoc)

No. at risk
Dacarbazine 338 244 173 111 79 50 24 4 0
Vemurafenib 337 326 280 231 178 109 44 7 1

Results: Efficacy

Patient 1: partial response in brain and liver

Patient 2: minor response confirmed by brain MRI and regression of liver metastases

~15 Years Later – How Have We Done?
Have our predictions/assumptions proved correct?

- Mixed Reviews on Efficacy:
  - Some very exciting: major gains, transforming disease outcomes.
  - Some modest -- but still practice changing
  - Many others negative -- or worse
Erlotinib NSCLC Results: TRIBUTE trial of Combination chemotherapy +/- Erlotinib

- **Median survival (months):**
  - Erlotinib: 10.6
  - Placebo: 10.5

- **1-year survival rate (%):**
  - Erlotinib: 46.9
  - Placebo: 43.8

- **Hazard ratio:**
  - Erlotinib: 0.995 (p=0.95)
NSCLC Overall Survival:
Standard: Chemo → Erlotinib
Experimental: Erlotinib → Chemo

- Median OS:
  - Standard: 12.0 (10.3 – 14.8) months
  - Experimental: 8.5 (7.2 – 10.5) months

- Hazard Ratio: 1.36 (95% CI 1.12 – 1.65)
- Log-rank test p = 0.002
~15 Years Later – How Have We Done? Have our predictions/assumptions proved correct?

- Mixed Reviews on Efficacy:
  - Some very exciting: major gains, transforming disease outcomes.
  - Some modest -- but still practice changing
  - Many others negative -- or worse
  - What are the adjuvant results of FDA approved targeted agents?
What are the adjuvant results of FDA approved targeted agents?

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Approved advanced disease indication</th>
<th>Adjuvant - status?</th>
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<tbody>
<tr>
<td>mTOR</td>
<td>everolimus</td>
<td>Renal</td>
<td>1 trial ongoing</td>
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<tr>
<td></td>
<td>temsirolimus</td>
<td>Renal</td>
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<tr>
<td>VEGF/VEGFR</td>
<td>bevacizumab</td>
<td>Colorectal</td>
<td>2 trials negative (CO-8, AVANT)</td>
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<td>Lung</td>
<td>1 trial not reported (E1505)</td>
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<td></td>
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<td>2 trials in GBM- not reported</td>
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<td>Breast</td>
<td>Several trials not reported</td>
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<td>sunitinib</td>
<td>Renal</td>
<td>3 trials - ongoing</td>
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<td>GIST</td>
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<tr>
<td>sorafenib</td>
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<td>axitinib</td>
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What are the adjuvant results of FDA approved targeted agents?

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<th>Adjuvant - status?</th>
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<tbody>
<tr>
<td>HER2</td>
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<td>Gastric</td>
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<tr>
<td></td>
<td>lapatinib</td>
<td>Breast</td>
<td>1 trial (ALTTO) not reported</td>
</tr>
<tr>
<td>EGFR</td>
<td>panitumumab</td>
<td>Colorectal</td>
<td>1 trial in rectal ongoing</td>
</tr>
<tr>
<td></td>
<td>cetuximab</td>
<td>Colorectal</td>
<td>1 trial – negative in RAS WT; worse outcome in RAS mut</td>
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<tr>
<td></td>
<td></td>
<td>Head and Neck</td>
<td>1 trial (RTOG 0920) ongoing</td>
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<tr>
<td></td>
<td>erlotinib</td>
<td>NSCLC</td>
<td>1 trial (RADIANT) not reported</td>
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<tr>
<td></td>
<td></td>
<td>Pancreas</td>
<td>2 trials ongoing</td>
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<tr>
<td></td>
<td>gefitinib</td>
<td>NSCLC</td>
<td>2 trials negative (BR19, S0023)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(gefitinib arm - worse outcome)</td>
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<td></td>
<td></td>
<td></td>
<td>1 trial recruiting in EGFR mut</td>
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<tr>
<td>Kit</td>
<td>imatinib</td>
<td>GIST</td>
<td>Trials positive for RFS &amp; OS</td>
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<td>EML4-ALK</td>
<td>crizotinib</td>
<td>NSCLC</td>
<td>?</td>
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</tbody>
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Summary Targeted Therapies – To Date: Toxicity and Efficacy in Common Solid Tumours

- **Efficacy:**
  - Advanced disease survival – some positive, mostly modest
  - Effects on long term survival (adjuvant) – with exception of trastuzumab and imatinib, so far all are negative

- **Toxicity:**
  - Common adverse effects of cytotoxics (hematological, hair loss) not generally seen
  - New types of adverse effects, some of which affect patient QoL: skin rash, fatigue, hypertension
How can we improve outcomes going forward?

- Potential Issues
  - Targets tackled
  - Agents and their dosing
  - Patient/tumour selection
  - Trial design
  - Drug resistance
  - The race to be “first” to market
  - Cost containment
Current thinking suggests that the model of linear cell signaling pathways should be replaced by one incorporating large, complex signaling networks in which cancer genes are often enriched in signaling “hubs.”
The whack-a-mole approach
The whack-a-mole game
A biosimilar

The whack-a-mole approach
The whack-a-mole approach
When Targeted Therapies Don’t Work
Every tumor has an escape plan.
mammalian TOR complexes

tuberous sclerosis proteins:
TSC1 (hamartin)
TSC2 (tuberin).
mTORc1 and mTORc2=mTORC1/2

Rheb = (Ras homolog enriched in brain) GTP-binding protein

Stephan Wullschleger,1,3 Robbie Loewith,2,3 and Michael N. Hall1TOR Signaling in Growth and Metabolism
Cell 124, February 10, 2006
Pharmacogenomics in Action
The Intricacies of Applying Genotyping to the Treatment of Patients

- Two ways in optimizing the ultimate efficacy and minimizing the toxicity of a therapeutic strategy:
  - antineoplastic agents specifically and prospectively targeted to molecular abnormalities within the cancers of individual Patients.
  - genetically defined features within the individual Patient’s normal, rather than tumor, molecular environment.
The Path Ahead
Eight Suggestions for the Next 15 Years

- Smarter target selection – more cancer specific
- Better drugs; more robust preclinical data
  - How much inhibition is enough? Is it achievable
  - Anticipate resistance
  - Consider alternative schedules of administration
- Adequate proof of concept in humans
  - Enough inhibition at safe doses to warrant development
- Invest in clinical biomarker development – early
The Path Ahead
Eight Suggestions for the Next 15 Years

- Set higher bar for efficacy in early clinical trials using meaningful clinical endpoints
- Don’t completely forget about cytotoxic chemotherapy
- Find the right balance between speed and perfection

Elizabeth A. Eisenhauer  NDDO Honorary Lecture, March 2012
The Path Ahead
Eight Suggestions for the Next 15 Years

- Set higher bar for efficacy in early clinical trials using meaningful clinical endpoints
- Don’t completely forget about cytotoxic chemotherapy
- Find the right balance between speed and perfection

Stay optimistic
- We have promises to keep and miles to go before we sleep…

Elizabeth A. Eisenhauer  NDDO Honorary Lecture, March 2012