Systemic Therapy in Chordoma

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Chordoma

- Rare
  - Incidence, 0.1/100,000/year
- Low-grade
- Sacrum, skull base + spine
- Median survival 6 years
- Resistant to conventional chemotherapy
- Imatinib 800mg per day
  - Inhibitor: PDGFR A + B, KIT

Casali P et al, Cancer 2004; 101: 2086-2097

Systemic therapy

- Conventional chemotherapy:
  - Inactive in Chordoma
  - Case reports of responses
- Phase II trial
- 9-nitrocamptothecin
  - N=15
  - One objective response
  - 33% median 6 month progression-free survival

Chugh R et al JCO 23; 3597-3604: 2005
Potential Targets

- **PDGFRB**
  - Frequently express PDGFRB\(^1\)
- **EGFR**
  - About 70% express EGFR\(^2\)
- **IGFR**
  - 40% evidence: activation IGF1-R/IR signaling\(^3\)
- **Brachyury**
  - Transcription factor: role in pathogenesis\(^4\)


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Imatinib

- 6 patients advanced chordoma
- **PDGFRB: RT-PCR**
  - Imatinib 800 mg per day\(^1\)
    - Improved pain control
    - Prolonged disease stabilization
    - Decreased contrast enhancement on CT
    - Decrease FDG uptake on PET
  - Imatinib + cisplatin\(^2\)
    - 2 out of 6: dimensional shrinkage


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Imatinib

- Phase II trial Imatinib
  - 50 evaluable patients. All PDGFRB (+)
    - RECIST response: 1 (2%)
    - 9 patients minor response
    - Clinical benefit rate: 64%
    - Median PFS: 9 months
      - 18 (+) months in patients stable at 6 months
    - No unexpected toxicity

Siacchiotti S et al, JCO 30(9): 914-920: 2012
Phase II: Imatinib

- N=50 patients with advanced chordoma
- RECIST
  - Partial response: 1/50 (2%)
  - Minor response: 9/50 (20%)
- Clinical benefit (CR/PR/SD ≥6 months)
  - 64.1% (95%CI 49.2–75.7%)
- Median PFS: 9 months
- PET Response at 3 months
  - N=30 patients: 39%

Stacchiotti S et al, JCO 30(9): 914-920: 2012

Imatinib + sirolimus

- N=10 chordoma patients
  - All progressed on imatinib
- 9 assessable for response
  - PR: 1
  - SD: 7
  - PD: 1
- Mean treatment duration 9 months

Stacchiotti S et al, Annals Oncology 2009; 20: 1886-1894

Sunitinib

- TKI: PDGFRB, KIT, FTL3, M-CSF
- Phase II trial in soft tissue sarcoma
- Chordoma:
  - 4 out of 9 (44%) chordoma patients
  - Durable stable disease1
- Sorafenib
- Case report of response in imatinib resistant disease2

1Garoge S et al J Clin Oncol 27; 3154-3160: 2009  
2Gelderblom H et al CTOS abstract 35162: 2008
EGFR inhibitors

- Epidermal growth factor receptor (EGFR) expression in 12 chordoma patients
  - Cetuximab and gefitinib
    - Sacral chordoma
    - Cervical chordoma
  - Erlotinib
    - Sacral chordoma

2Hof H et al Onkol 29; 572-574: 2006
3Linden O et al Acta Oncol 48; 158-159: 2009
4Singhal N et al Anti-Cancer Drugs 20; 953-955: 2009

Phase II: Lapatinib

- Oral TKI EGFR + HER2 (1500mg daily)
- N=18 patients, advanced chordoma
  - EGFR (+)
  - Choi assessment:
    - Response: 6/18 (33%)
    - Median PFS: 6 months (IQ range: 3-8)
  - RECIST:
    - No responses
    - Median PFS 8 months (IQ range 4-12)
  - Median OS: 25 months (IQ range: 23-26)


MRI scan: pre- and post-treatment with cetuximab and gefitinib.
The arrows indicate the spinal cord.

Linden O et al Acta Oncol 48; 158-159: 2009
For discussion

• Everolimus + imatinib: Italy – closed
  – If trial positive: Submission for approval
• EMA meeting
• Access: variability across Europe
• Clinical Trials:
  – EGFR inhibitor + other
  – Phase I trials,
• Collaboration
  – Guidelines: Lancet Oncology, ESMO, NCCN
  – Translating laboratory findings - clinic

Conclusions

• Chordoma: challenging disease to treat
• Conventional chemotherapy inactive
• Unmet medical need
• Prospective translational studies: collaboration