Osteosarcomas

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Osteosarcoma

• Most common primary malignant bone tumor
• Neoplastic cells produce osteoid
• Before chemotherapy almost always fatal
  – Now long term survival 60-65%
• Urgent need to identify effective therapeutic agents

Epidemiology

• Annual incidence = 5 per million
  – 1000 new cases per year in USA
• Usually during puberty
  – Peak incidence 10-14 years
  – Time of rapid bone growth
  – Very rare in children <5 years
• Older patients
  – Paget’s disease
  – Radiation

Radium watch dial painters
1917-1926 U.S. Radium Corporation
Bimodal Age Distribution

Etiology Largely Unknown

- Genetic Syndromes
  - Li Fraumeni
    - TP53 mutation
    - 6% incidence of OS
  - Hereditary retinoblastoma
    - RB1 mutation
  - RecQL4 helicase family
    - Rothmund-Thompson and related repair syndromes
Other Associations

• Paget’s disease
  — Several thousand fold risk
• Radiation therapy
  — Dose dependent
• Fibrous dysplasia
• Hereditary exostosis
• Ollier’s disease

Classification of Osteosarcoma

Conventional
• Osteoblastic
• Chondroblastic
• Fibroblastic

Variants
• Telangiectatic
• Small cell
• Low-grade central
• Paget’s sarcoma
• Radiation-associated
• Gnathic
• Bone surface
  — Periosteal
  — High-grade surface
• Extraskeletal

Osteoblastic Osteosarcoma
Differential Diagnosis: Chondrosarcoma

- Bone may be sparse in chondroblastic OS
- Peripheral condensation / spindling in OS
- IDH1 and IDH2 mutations in chondrosarcoma
Fibroblastic Osteosarcoma
Giant Cell Rich Osteosarcoma

Telangiectatic Osteosarcoma
Low-grade Central Osteosarcoma
Low-grade Central Osteosarcoma

- Molecular biology
  - Simple karyotype
  - MDM2 gain/amplification
  - Low frequency of TP53 mutations
- Excellent prognosis
  - 90% 5-year survival
- Dedifferentiated in 10-36%

Differential Diagnosis:
Fibrous Dysplasia

| Low-grade Central Osteosarcoma | Fibrous dysplasia |
Dedifferentiated Low-grade Central Osteosarcoma
Radiation-Associated Osteosarcoma

- Latency period
  - Average 7-8 years
  - Sometimes 30-40 years
- Prognosis
  - Aggressive tumor
  * Due to axial location?

Post-Radiation OS in Cervical Cancer

Gnathic Osteosarcoma
Gnathic Osteosarcoma

- 6-10%
- Older age
- Mandible = maxilla
- Often low-grade / often chondroblastic
- Better prognosis
  - 77% 5-year survival
  - Lower metastatic rate
  - Locally aggressive
  - Chemotherapy unproven
- Radiation-associated tumors more aggressive

Osteoblastic Osteosarcoma

Chondroblastic Osteosarcoma of the Mandible
Low-grade Osteoblastic Osteosarcoma

Radiation-Associated Gnathic Osteosarcoma
- 54-year old Woman
- Radiotherapy 8 years ago for Merkel cell carcinoma of the cheek
- DOD pulmonary metastases

p53
Bone Surface Osteosarcomas

- Parosteal
- Periosteal
- High-grade surface

Parosteal Osteosarcoma

- Rare (4%)
- Young adults
- Ossifying mass on bone surface
  - Classic location posterior distal femur
  - Underlying cortical sclerosis
- Usually low-grade
- 25% invade medulla
- Dedifferentiation (15%)
Medullary Invasion in Parosteal Osteosarcoma
Parosteal Osteosarcoma with Cartilage

Parosteal Osteosarcoma Karyotype

MDM2
Dedifferentiated Parosteal Osteosarcoma

- Very rare
- Fusiform mass, diaphysis, saucerizes cortex
- Tibia most common
- Chondroblastic, intermediate grade
- Good prognosis
  - 15% metastatic rate

Periosteal Osteosarcoma

- Very rare
- Fusiform mass, diaphysis, saucerizes cortex
- Tibia most common
- Chondroblastic, intermediate grade
- Good prognosis
  - 15% metastatic rate
High-grade Surface Osteosarcoma
Extraskeletal Osteosarcoma

Treatment of Osteosarcoma

• Pre-1970
  — Believed to be chemo-resistant
  — Amputation followed by pulmonary metastases in 80-90% of patients within 6-12 months
  — <20% survival rate

  “If you do not operate, they die. If you do operate they die just the same—gentlemen this meeting should be concluded with prayers.”

  Sir Stanford Cade

Chemotherapy

• 1970’s
  — Introduction of high dose methotrexate
  — Objective to destroy putative “silent pulmonary metastases”
  — 40% survival
  — Combined with doxorubicin survival improved

Mayo Clinic refuted benefit of chemotherapy, noting improved survivals compared to historical controls, suggesting natural history of the disease was changing.
Multi-Institutional Osteosarcoma Trial

- 1982-86
- Amputation followed by either chemotherapy or observation
- Treatment group: 65% disease-free survival
- Control group: <20% disease-free survival

Results confirmed there had been no change in the natural history of the disease.

Neoadjuvant Chemotherapy and Limb Salvage Surgery

- Effective neoadjuvant chemotherapy coincided with improvements in surgical technique
- Now-a-days >80% patients treated by limb salvage surgery

Pulmonary Metastasis

- 90% of metastases are pulmonary
  - 10-20% synchronous
  - 40% metachronous
  - 20% 5-year survival
- Resection of isolated pulmonary metastasis correlates with survival and cure in select patients
Multidisciplinary Tumor Board

Current State

- We have reached a therapeutic plateau
  - 5-year survival unchanged since 1980’s
  - No added benefit from intensifying chemotherapy or adding new agents
- Many patients continue to die from metastatic disease
- Urgent need to better understand its biology and develop novel therapeutic agents
Cytogenetics

- Tremendous complexity
- Pronounced inter- and intra-tumoral heterogeneity
- Genetic gains, losses and amplifications
- Marker chromosomes
- Whole chromosomal alterations
  - esp. +1, -9, -10, -13, -17
- Frequent rearrangements
  - 1p11-13p, 1q11-12, 1q21-22, 11p14-15, 14p11-13, 15p11-13 and 17p

Complex Karyotype in Osteosarcoma

Disruption of Tumor Suppression

- Alterations of TP53 and RB1 pathways consistent feature
  - Important cell cycle regulators
- Mutated in 20-35% and 50-95%, respectively
- Secondarily altered by mechanisms other than mutations
  - Molecular effects from other pathways
  - Epigenetic events
    - Methylation, histone modification, miRNA
**Deregulation of Transcription**

- Excess production/over-activation of various transcription factors
  - Up-regulation of FOS and JUN
  - MYC amplification
  - RUNX2
  - Others

**Growth Factor Receptor and Other Signaling Pathways**

- Broad array of pathways activated/implicated in osteosarcoma
  - TGF-β, BMP, IGF, FGF, CTGF, PTH, HER2, ERBB4, FAS, Notch, Wnt/β-catenin, Ret, Axl, MMP, Osterix, TWIST, Hippo/YAP, etc.
- Redundancies and interdependencies

**Drug Resistance**

- Major challenge in treating osteosarcoma
  - 35-45% become unresponsive to chemotherapy
  - Major issue with pulmonary metastases
- Proposed mechanisms
  - Perturbations in signal transduction
  - Drug efflux (p-glycoprotein)
  - Impaired transport into cell
  - Detoxification
  - Alterations of topoisomerase II
  - Increased DNA damage repair
  - Multidrug resistance associated protein
- No prognostic value / effective remedies to date
Genomic Profiling

- Major candidate genes in pathogenesis
  - Gains 1p36, 1p21-22, 6p12-21, 8q21-24, 12q11-14, 17p11-13, 19q12-13
  - Losses 3q13, 8p21, 9p13, 13q14

- Deletion and LOH 3q13
  - LSAMP
    - Progression and poor survival
- Amplification 6p12-21
  - RUNX2
    - Osteoblastic differentiation
    - Poor response to chemotherapy
  - VEGFA
    - Angiogenesis

- Amplification/gain 8q24.21
  - MYC

Whole Genome Sequencing

- High rates of structural variations and copy number alterations
  - Single nucleotide variations (SNVs) non-recurrent
- Chromosomal lesions (not SNVs) = major mechanism of recurrent mutations
  - Significant chromosomal lesions involve known cancer genes
    - Notably TP53, RB1 and ATRX

Whole Genome Sequencing

- TP53 most frequently mutated gene
- Almost all tumors show alterations of TP53 pathway
- Both alleles (80%)
- MDM2 amplification (10%) inhibits TP53
- Major oncogenic driver in osteosarcoma
- Genomic instability
  - Underlying mechanism to initiate and promote osteosarcomagenesis
  - Precedes TP53 inactivation
- Multiple clones common (61%)

Prognostic Markers

- No biologically-based validated factors have been identified
- Factors associated with poor prognosis:
  - Metastatic disease
    - Osseous worse than pulmonary
  - Recurrent disease
  - Axial location
  - Radiation
  - Paget’s disease

Histologic Response to Chemotherapy

- Most important prognostic factor to date
- Percent Tumor Necrosis
  - Good response (>90%)
    - 70-80% 5-year survival
  - Poor response (<90%)
    - 35-40% 5-year survival
Novel/Emerging Therapeutic Strategies

- Novel drug delivery mechanism
  - Aerosolized compounds for pulmonary metastases
- Overcoming drug resistance
  - Inhibit drug efflux
  - Novel antifolates

Altering Tumor Environment

- Inhibition of osteoclast-mediated bone destruction
  - Bisphosphonates
  - RANK-ligand inhibitors (denosumab)
- Inhibition of angiogenesis
  - VEGFR inhibitors
- Controlling metastases
  - Inhibiting Ezrin
  - Modulating FAS expression

Molecular Targeted Approaches of Signaling Pathways

- Inhibition of receptors/transduction
  - IGF pathway
  - mTor pathway
  - Src pathway
  - Notch pathway
  - PI3K/Akt pathway
Other / Emerging Strategies

- Immunomodulation
  - Check point inhibition
- Epigenetic modification
- miRNA and lncRNA targeting
- Oncolytic viruses
- Bone-seeking radio-pharmacy
- Nanoparticle technology

Osteosarcoma-Summary

- Etiology largely unknown
- Wide histologic variability
- Complex molecular biology
  - High genomic instability
  - No specific biomarkers
  - Tremendous redundancy in molecular pathways and complex interactions
  - Epigenetic modifications
- Extremely difficult to place it in a single biological construct

Osteosarcoma-Summary

- Although effective, traditional chemotherapy has reached a therapeutic plateau
- Personalized medicine
  - Elucidate genetic and epigenetic landscape of individual tumors
  - Identify specific molecular targets
- Immunomodulation
  - Early studies show potential promise
Thank you