ANAPLASTIC THYROID CANCER

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Grand Rounds Presentation
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Anaplastic Thyroid Cancer (APC)

- One of the most aggressive malignancies
- Survival measured in months
- Rare (2 per million per year)
- 1.6% of all thyroid cancers
- Often associated with well differentiated thyroid cancers (evidence of dedifferentiation, <1%)
  - History
  - Path
- Incidence declining
  - IHC staining in ’80s
  - Iodination of food
  - More aggressive treatment on WDTC
Clinical Presentation

- 60’s-70’s
- 55-77% female
- Most patients present with rapidly enlarging neck mass (mean size at presentation 8cm)
- Some incidentally discovered
- Local compressive symptoms
- Cervical lymphadenopathy in >40%
- 30% with TVC paralysis
- 90% with direct invasion
- 50% present with distant metastasis
- 75% develop distant mets during course of disease
  - Lung 80%, Bone 6-15%, Brain 5-13%, Intestine
Diagnosis

- FNA accurate in 90%
- Unencapsulated
- Tan-white
- Direct extension into soft tissues
- No radioactive iodine uptake
- CT to eval extent
Pathology

- Microscopically 3 histologic patterns (no prognostic difference)
  - Spindle
  - Giant-cell
  - Squamoid

- Previous nomenclature
  - Small cell (lymphoma)
  - Insular cell (morphology)
Molecular Pathology

- NM23 deletion
  - Metastasis suppressor gene
- P53 mutants found in 14% of all thyroid cancers—more commonly in APC
  - Loss of genome stability
Prognostic Factors

- Distant mets (Vankatesh): 8mos vs 3mos
- Acute symptoms, tumor >5cm, distant mets, leukocytosis (Sugitani): Multivariate analysis reveals each an independent risk factor
- Longer duration of symptoms, tumor <10cm, incidental findings within WDTC (Ojeda): better prognosis overall
Treatment

- Surgery
- Radiation
- Chemotherapy
- Multimodality
Surgery: Controversial

● Mayo Clinic: 50 year experience (134pts)
  ● Neither the extent of operation nor the completeness of resection had a significant impact on survival

● Kobayashi: 37 patients
  ● Removal of macroscopic disease increased survival from 2mos to 6mos
Radiotherapy

- Local control
- ATC relatively radioresistant
- Treatment morbidity
- Palliative local control achieved 68-80%
- Levendag: 51 patients receiving >30Gy had median survival of 3.3 months. <30Gy had median survival of 0.6 months.
- Junor: no survival benefit with radiation therapy, despite 80% initial response and 39% initial complete response.
Chemotherapy: Monotherapy

- Treatment of distant mets
- Unsuccessful at altering the fatal outcome of ATC
- Doxorubicin: (most frequent) <20% response rate and no evidence of complete response.
- Ain: 53% response rate in a Phase II trial using paclitaxel.
  - All eventually died of their disease
  - Median survival 24 weeks
  - Responders to paclitaxel: 32 weeks, nonresponders: 7 weeks.
  - Stimulated further study
Chemotherapy: Combination

- Doxorubicin, bleomycin, cyclophosphamide combination: very little effect in multiple studies
- Yeung: combination of paclitaxel and manumycin (farnesyl:protein transferase inhibitor) enhanced cytotoxic effect and increased apoptotic cell death in vitro and in vivo.
  - Inhibits angiogenesis
  - Apoptosis regulatory pathway.
Multimodality Therapy

- Tennvall: 33 patients treated with hyperfractionated radiotherapy, doxorubicin followed by surgical debulking.
  - Local control achieved 50%
  - Only 24% death due to local failure
  - Median survival only 4.5 mos
  - Only 4 survived >2 years
Multimodality Therapy

- Sugino: 40 patients retrospectively evaluated
  - Improved 1 year survival with surgical debulking + radiation vs radiation only (60% vs 20%)
  - “Debulking”: thyroidectomy for WDTC with foci of ATC
Multimodality Therapy

- MD Anderson: 121 patients
  - 12 patients with complete macroscopic resection of tumor survived longer than 24mos.
  - 10/12 post op chemo and radiation
Multimodality Therapy

- Haigh: 26 patients surgical resection (retrospective)
  - 8 resection for cure, no residual or minimal residual disease
    - Median survival 43 months
  - 18 palliative resection
    - Median survival 3 months
  - Both groups received post op radiation, chemotherapy or both.
  - Selection bias
Future Investigations

- More detailed understanding of dedifferentiation at the molecular level
- Better understanding of genes involved in regulatory pathways
- Chromosome mapping studies
  - Chromosome 7 and 16
- Clinical trials involving gene therapy
Current Molecular Investigations

- Adenovirus-mediated p53 gene therapy shown to increase chemosensitivity to adriamycin and doxorubicin
- Bone morphogenic protein (BMP-7) shown to inhibit proliferation of ATC cells by G1 arrest
- Bovine seminal ribonuclease induced highest rate of apoptosis in ATC cells
  - Injection into nude mice with established ATC tumors resulted in complete regression of tumor
Histone deacetylase inhibitors: promote apoptosis and differential cell cycle arrest in ATC cells

Human sodium iodide symporter (hNIS): when transfected into ATC cells, *in vitro* and *in vivo*, established uptake of iodide.
Summary
References

- Sugino, K et al. The important role of operations in the management of anaplastic thyroid carcinoma. Surgery 2002, 245-248.