DIFFICULT CASES IN SARCOMA

Epithelioid Sarcoma and Alveolar Soft Part Sarcoma

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General Principles

• Very rare sarcomas

• Group of selected subtypes which have:
  – Distinctive clinical behaviour
  – Distinct biologies and/or molecular characteristics
  – Responses to agents targeting these pathways
    • Or a lack of response to conventional cytotoxics
Case 1

24 yo single man

– Computer programmer.
– Living at home with elderly parents
– No Past History of note. No Family History of cancer

• Referred to Peter MacCallum Sarcoma Service from regional hospital, 1-month post complicated resection of a distal thigh soft-tissue mass arising from left high.
24 yo man

- Suboptimal (R1) resection, approx. 3cm tumour
- Sarcoma NOS by local pathology service
- Pathology reviewed at Peter Mac
  - High grade sarcoma, morphologically consistent with epithelioid sarcoma or synovial sarcoma. Distal margin+ve
  - Expression of cytokeratin, epithelial membrane antigen, vimentin and CD34. Neg for S100, CD31. FISH -ve for t(X:18)
  - Features consistent with epithelioid sarcoma
24 yo man: epithelioid sarcoma

Next Steps:

• Restaging completed. MRI left thigh, CT-C/A/P
  – No clear evidence of residual tumour
  – No locoregional or distant metastatic disease

• Further management?:
24 yo man: epithelioid sarcoma

• Further management?:
  – Wide-Resection. Limb-sparing vs amputation?
  – Radiotherapy- pre vs post-op?
  – Systemic therapy?
24 yo man: epithelioid sarcoma

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• Went on to receive External beam RTx

• Surgical re-resection with wide margins
  – No residual tumour evident

• Adjuvant chemotherapy not recommended
  – Given histology and lack of clear OS benefit
24 yo man: epithelioid sarcoma

• Routine follow-up

• Nine months later:
  – Painful subcutaneous lesions distal thigh
  – Deep and infiltrative on imaging with MRI
    • Within radiation field
    • At distal end of prior tumour
    • No proximal extension
  – Biopsied
    • Recurrence confirmed
  – Increasing pain++ with ulceration of superficial disease
24 yo man: epithelioid sarcoma

• Further management?:


24 yo man: epithelioid sarcoma

- Further management?:
  - Re-resection not thought possible
    - Above knee amputation performed
  - Remained disease-free for further 3 years
    - Now in 6-monthly follow-up
  - Re-presents with multiple subcutaneous lesions
  - Extending proximally
    - Painful superficial lesions and sacral pain++
    - Clinically, growing very rapidly
Recurrent epithelioid sarcoma

• Further management?:

![Image of recurrent epithelioid sarcoma](image-url)
Recurrent epithelioid sarcoma

• Restaging: Locoregional disease on PET/CT

• Further management?
  – Radiotherapy considered,
    • but concerns given in-field recurrence and rapid proximal progression
  – Commenced on chemotherapy with Dox/Ifos
Metastatic epithelioid sarcoma

- Dox/Ifos: initial stabilisation after 2 cycles, followed by further progression at C4

- Enrolled onto a Phase Ib clinical trial with Docetaxel and a novel PDGF inhibitor
Metastatic epithelioid sarcoma

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Metastatic epithelioid sarcoma

• Disease control on and off therapy for additional 9 months

• Progression with proximal abdominal and nodal disease
  – Eventual lung metastases
  – Died from complications of metastatic disease
Metastatic epithelioid sarcoma: Take home messages

• What should/could have been done differently?
  – Initial surgery
  – Radiotherapy? And re-resection?
  – Follow-up? Imaging
  – Challenges with continued proximal migration of disease

• Use of systemic chemotherapy for met disease
  – Other options?
  – Molecular drivers/molecular testing?
    • Multiple targets implicated including EGFR, cyclin D1, VEGF, mTOR
Metastatic epithelioid sarcoma: Literature/Data

- No meaningful prospective data. Retrospective:
  - 1) Royal Marsden (R Jones et al. Am J Clin Oncol. 2012 Aug),
    - 1990-2009 database
    - Proximal vs Distal
    - 55 patients, 20 treated with chemotherapy (Dox+/-Ifos)
      - Partial responses in 25%, but short-lived
  - Lots of anecdotes, and individual patient responses on trials with agents including pazopanib, eribulin, navelbine, trabectedin

- Take home message: explore novel options early, sequential single agents
Case 2

27 yo married woman, 2 yo child

– No Past History of note. No Family History of cancer

– Presents with right forearm lesion, present for at least 12 months, slowly growing

– Staging CT scans demonstrate 3 small pulmonary metastases,
  • RLL x 2 and LUL:. 10, 9 and 7mm in size
  • FDG avid on PET

– Biopsy of left forearm lesion:
Case 2: 27 yo woman

- Biopsy of left forearm lesion:
- Nests of epithelioid cells separated by fibrovascular septae and vascular channels
  - “Pseudo-alveolar pattern”

- Diagnosis of Alveolar Soft Part Sarcoma
Case 2: 27 yo woman

- Resection of forearm lesion

- Options for management of pulmonary mets discussed including
  - Staged resection
  - Watch and wait
    - Staged resection for diagnostic and treatment purposes
    - Confirmed as metastatic disease
Case 2: 27 yo woman

- Over following 3 years
  - 2 further resections for single/oligometastatic disease.
  - All via wedge resections

- Now presents with
  - multiple lung metastases (approx 10 lesions), largest 5mm
  - Bone metastasis with scapulae metastasis
    - Symptomatic
    - Treated with Radiotherapy (palliative)
Case 2: 27 yo woman

- Options for management of systemic disease?
  - Systemic chemotherapy
  - Watch and wait
  - Other options?
Alveolar Soft Part Sarcoma

• Incidence: approx 0.5-1/100,000
• Adolescents/Young adults
  – Female>male
  – Natural history variable,
    • High metastatic rate,
    • Often to atypical sites (brain, bone, soft tissue)
    • But metastases often indolent in their behavior,
      – Multiple surgical resections may be appropriate.
    • Can grow to a certain size, and then remain indolent.
    • Therefore Patient’s Natural History very important
Alveolar Soft Part Sarcoma

- Median survival with metastatic disease approx 36 months cf metastatic STS

- Characterised by an unbalanced translocation t(X;17)(p11:p25) which results in the fusion of the ASPL and TFE3 genes.
- Resulting in unregulated transcription of TFE3 controlled genes.
- Strong expression of angiogenic factors
Expression in ASPS

Stockwin et al. (2009) *BMC Cancer*
VEGF inhibition in ASPS: Initial “anecdotes”

**Sunitinib:** 4 evaluable patients on compassionate use protocol
- 2 Partial Responses, 1 SD, 1 PD
  (Stacchiotti et al. (2009) *Clinical Cancer Research*)

**Cediranib:** 7 patients on two Phase I studies
- 4 Partial Responses, 2 Minor Responses, 1SD
CASPS: A phase II trial of Cediranib in the treatment of patients with ASPS

- To confirm the ability of cediranib to halt disease progression in patients with metastatic ASPS at 24 weeks after randomisation & to produce objective response according to RECIST criteria.
- Randomised 2:1 to receive cediranib or placebo;
  - At 24 weeks, Rx will be unblinded after which all pts on placebo will be given cediranib.
- Primary endpoint week 24 percentage change in the sum of target marker lesions from randomisation.
- Led by Ian Judson (ICR): global collaboration including 2 sites in Australia
Conclusions

- Increasing number of very rare sarcoma subtypes with distinct biology, clinical behaviour
- Diagnostic accuracy critically important
- Clinical guidance critically important
- Given the impact on that patient
- International sarcoma network leading the way for other rare cancers/rare subtypes
  - Help provide diagnostic and clinical guidance
  - Conduct appropriate clinical trials