Perivascular epithelioid cell tumours (PEComa) are a group of sarcomas that exhibit a myomelanocytic phenotype and share a distinctive cell type, the perivascular epithelioid cell. Major subtypes include lymphangioleiomyomatosis (LAM), angiomyolipoma (AML) and PEComa. The latter subtype is rare and occurs sporadically in the gastro-intestinal tract, retroperitoneum, uterus or somatic soft tissues. They are composed of nests and sheets of epithelioid or spindled cells and are intimately related to blood vessel walls (1).

Most PEComas are benign and do not occur after complete surgical resection. However a small subset of PEComas demonstrate malignant behavior with local recurrences or distant metastases. There is no standard therapy for the treatment of malignant PEComa (1).

Sirolimus (Rapamune™; Pfizer) is a selective immunosuppressant that inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a critical kinase for cell cycle progression (2). Some benefit has been observed in the treatment of a small sample of patients with LAM and AML with sirolimus. Since these tumours share activation of the mTOR pathway, the rationale is that sirolimus could produce similar clinical benefits in patients with PEComa (an off-label indication) (1).
Epidemiology

No relevant epidemiological data were identified. An unpublished review article reported 234 cases (116 reports) of PEComa (all subtypes in the English literature). Of the 38 cases of recurrence, 31 were classified as malignant. At the time of the review, only three of these cases were treated with sirolimus (3).

Published data

There are no randomised controlled studies evaluating any treatment, including sirolimus, for the management of PEComa. The published evidence base is limited to case reports and case series – these focus more on the presentation and distinguishing pathological features of the disease. This evidence review has addressed the treatment of PEComa (not LAM or AML) with sirolimus and these data have been described below:

An unpublished abstract presented at the American Society of Clinical Oncology (ASCO) described a case series of seven patients with malignant PEComa who were treated with sirolimus or temsirolimus (4). [Absolute data were not available within the abstract for each individual case.]

Five patients were female and the median age was 46 years. The most common primary site was the gastrointestinal tract (29%) and two patients had metastatic disease at baseline. Six patients received sirolimus (median starting dose, 3 mg daily to a median highest dose, 4 mg daily). Therapeutic drug monitoring was not performed.

Overall, best responses by computed tomography (CT) scan were partial response: 3 (43%), stable disease: 2 (29%) and progressive disease (PD): 1 (14%). One patient only received 7 days of sirolimus therefore was not evaluable.

Two patients continued on treatment, three stopped due to PD, one stopped due to grade 3 thrombocytopenia and one due to grade 3 cough, but two weeks later had confirmed PD on CT. One patient experienced a grade 3 trigeminal nerve pain leading to dose reduction in sirolimus (4).
## Case reports of sirolimus use for PEComa

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age/sex</th>
<th>Disease history</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/M</td>
<td>20cm PEComa in retroperitoneum, resected in 2005. Retroperitoneal recurrences, further resection in 2007. Additional sites of disease noted 3 months later. Participated in phase I study of oral inhibitor of MET and developed disease progression.</td>
<td>In 2008, treated with sirolimus 8mg daily (trough level 36ng/ml).</td>
<td>Significant reduction in size of all tumours with almost complete resolution at one year. Treatment and response ongoing at 16 months of follow up.</td>
<td>Mild fatigue</td>
</tr>
<tr>
<td>1</td>
<td>70/M</td>
<td>9cm renal PEComa. Six years later, local recurrence treated with sunitinib but disease progression.</td>
<td>In 2008, treated with sirolimus 4mg daily but dose reduced to 1mg on alternate days due to adverse events (trough level 36ng/ml).</td>
<td>40% reduction in the longest diameter and 10 month disease control before disease progression (trough level 9.4ng/ml). Subsequent resection and remains alive with disease.</td>
<td>Diarrhoea and fatigue</td>
</tr>
<tr>
<td>1</td>
<td>61/F</td>
<td>9cm malignant PEComa in cervix with pulmonary metastases</td>
<td>Sirolimus 4mg daily (trough level 5ng/ml) but disease progression. Dose increased to 8mg daily but further disease progression (trough level 7ng/ml). Dose reduced to 2mg daily with addition of clarithromycin to decrease metabolism of sirolimus (trough level 20ng/ml).</td>
<td>Stable disease for most lesions and reduction in size of some nodules. One month later, significant disease progression treated with sorafenib 200mg twice daily and sirolimus 4mg daily. Two months of disease control but patient died after worsening of pulmonary parenchymal disease</td>
<td>Not reported</td>
</tr>
<tr>
<td>5</td>
<td>46/F</td>
<td>9cm malignant broad ligament PEComa in cervix</td>
<td>Considered unresectable. Patient started sirolimus 4mg daily</td>
<td>After two years of sirolimus, tumour reduced to 5.3cm.</td>
<td>Mouth ulceration with 5mg daily</td>
</tr>
<tr>
<td>6</td>
<td>2/F</td>
<td>12cm PEComa in abdomen. Initial treatment with chemotherapy but no response. Imatinib started but stopped due to adverse events</td>
<td>Considered unresectable. Sirolimus with etoposide started [treatment details not stated]</td>
<td>Partial reduction of liver lesions. Debunking surgery undertaken but residual disease</td>
<td>No relevant toxicity reported</td>
</tr>
</tbody>
</table>
Sirolimus is administered orally. The dose for the prophylaxis of organ rejection in adult patients receiving a renal transplant (licensed indication) is a 6 mg oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily until results of therapeutic monitoring are known. The dose should then be individualised to obtain whole blood trough levels of 4 to 12 ng/ml. For maintenance therapy, dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/ml (2).

The cost of sirolimus (30 tablet pack) is
500mcg: £69
1mg: £86.49
2mg: £172.98

The average cost per cycle (using BSA 1.75m², ABW 80kg, and VAT at 20%): £288-576 per patient per month (30 days) based on dose range 3-6mg.

*personal communication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>Malignant PEComa</td>
<td>Assumed 1-2 cases referred within London region (8.2 million population) which is equivalent to 0.012-0.024/100,000*</td>
<td>Variable but worse case scenario is 24 months which would cost from £6,912-£13,824 per person</td>
<td>Cost for one case would be £82.94-£331.78</td>
</tr>
</tbody>
</table>

**Summary**

PEComas are a rare group of tumours with a distinct underlying cell type. The majority of these tumours are benign and removed by surgical excision; however there is a small subset of PEComas that are malignant.

Ideal treatment strategies remain undefined but there could be an emerging role for the use of sirolimus for resected malignant tumours. Published literature in the form of case reports/series suggests that patients (n=11) may achieve some disease control or reduction of tumour burden following treatment with sirolimus. However because of the small numbers of cases reported and the limitations of these data, further investigation in the form of clinical trials is required to define the role of sirolimus with respect to optimal dosing regimen, treatment duration and place in therapy. Given the rarity of these tumours, this approach may not be feasible.
Sirolimus for malignant perivascular epithelial cell tumours (PEComa)

References:


3. Bleeker JS, Quevedo JF, Folpe AL. “Malignant” Perivascular Epithelioid Cell Neoplasm: Risk Stratification and Treatment Strategies. Mayo Clinic; Accepted 8 February 2012 (unpublished review article)

4. Vitfell-Pedersen J, Benson C, Tunariu N et al. A retrospective study from the Royal Marsden Hospital (RMH) of patients with malignant perivascular epithelioid cell tumours (PEComa) receiving treatment with sirolimus (SI) or temsirolimus (TSI). JCO 2012 (suppl; abstr 10038). http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=93255


Details of search strategy:

NeLM; MIDB; EMC; Cochrane; NICE; SMC; AWMSG; NCCN; ASCO; ASH; ESMO

1. EMBASE; exp RAPAMYCIN/; 29727 results.
2. EMBASE; exp PERIVASCULAR EPITHELIOID CELL TUMOR/; 220 results.
3. EMBASE; 1 AND 2; 14 results.
4. EMBASE; 3 LIMIT TO: English Language and Humans; 13 results.
5. MEDLINE; exp SIROLIMUS/; 11599 results.
6. MEDLINE; exp PERIVASCULAR EPITHELIOID CELL NEOPLASMS/; 2274 results.
7. MEDLINE; 5 AND 6; 64 results.
8. MEDLINE; 7 LIMIT TO: English Language and Humans; 60 results.
9. EMBASE, MEDLINE; Duplicate filtered: [3 LIMIT TO: English Language and Humans], [7 LIMIT TO: English Language and Humans]; 73 results.

The document reflects the views of LCNDG and may not reflect those of the reviewers

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