Therapies for the Medical Management of Persistent Hypoglycaemia in Two Cases of Inoperable Malignant Insulinoma: Case Reports and Review of the Literature.

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Running Title: Hypoglycaemia in Inoperable Malignant Insulinoma.

Word Count: 3274 (abstract 167 + body text 2803 + captions 304). Excludes references (974) and tables.
ABSTRACT.

Objective: Hypoglycaemia poses a significant management challenge in patients with unresectable functional malignant insulinoma. Novel agents such as mTOR inhibitors and radiolabelled peptides may be effective where there is failure of conventional therapy.

Design: We present the cases of two men diagnosed with inoperable malignant insulinoma and hepatic metastases who developed severe symptomatic hypoglycaemia, and review potential therapies for glycaemic support.

Method: Despite treatment with diazoxide, frequent oral carbohydrate, prednisolone and somatostatin analogue therapy, both men required hospital admission for treatment with continuous intravenous dextrose. Both were treated with Lutetium-177 octreotate. One man also commenced Everolimus, an mTOR inhibitor.

Result: Use of Lutetium-177 octreotate, and in one case Everolimus, successfully achieved normoglycaemia facilitating safe discharge from hospital. Both men also had regression in the size and number of hepatic metastases.

Conclusion: Lutetium-177 octreotide and everolimus are options for managing hypoglycaemia due to unresectable malignant insulinoma when refractory to conventional supportive therapies.

Keywords: Insulinoma, neuroendocrine tumour, hypoglycaemia, lutetium, everolimus, diazoxide, octreotide, octreotide, somatostatin, glucocorticoid, prednisolone, temozolomide, capecitabine.
INTRODUCTION.

Neuroendocrine tumours of the pancreas occur infrequently, with an incidence of 1 to 1.5 per 100,000 in the United States [1]. Of those, 20-30% are insulinomas [2], the vast majority being benign. Symptomatic hypoglycaemia is the major clinical manifestation of insulinomas. Where possible, surgical resection is the optimal treatment [1,2] with prior supportive therapy. However, 10-15% of insulinomas are malignant. Patients with significant hypoglycaemia and inoperable metastatic disease can be difficult to manage. We present the cases of two patients with inoperable malignant insulinoma, documenting the steps taken to treat persistent severe hypoglycaemia, and review the literature.

CASE REPORTS.

Case 1.

A previously well 64 year old man presented with hypoglycaemia, initially manifesting as severe nocturnal hunger. Plasma c-peptide, insulin and glucose levels were consistent with endogenous hyperinsulinaemia (Table 1). There was no evidence of multiple endocrine neoplasia type 1.

Computed tomographic (CT) imaging identified two masses in the body and tail of the pancreas, with multiple hepatic metastases. Endoscopic ultrasound and biopsy confirmed malignant insulinoma. Radiolabelled Indium-111 octreotide scintigraphy demonstrated avidity of the lesions for octreotide. The extent of hepatic involvement precluded resection or ablation.

Hypoglycaemia persisted despite outpatient treatment with diazoxide (up to 200mg x3/day), prednisolone (40mg daily) and subcutaneous octreotide (up to...
500µg/day in three divided doses). A hypoglycaemic seizure necessitated hospital admission and continuous intravenous 25% dextrose infusion.

The patient was treated with intravenous radiolabelled Lutetium-177 [DOTA\(^0\),Tyr\(^3\)] octreotate with concurrent amino acid infusion for nephroprotection. Inpatient support was still required subsequently, with intravenous dextrose (up to 600g/day), prednisolone, nocturnal nasogastric feeding and a continuous subcutaneous octreotide infusion (up to 3000µg/day) necessary to maintain near normoglycaemia.

As it was not possible to safely cease continuous intravenous dextrose therapy, everolimus (2.5mg x2/day) - an mTOR inhibitor - was commenced, with rapid glucose response (Figure 1). Complications potentially attributable to everolimus therapy are summarised in Table 2. These conditions resolved without dose reduction of the everolimus. Intravenous dextrose infusion was ceased nine days after everolimus was commenced, without further episodes of hypoglycaemia, and with decreased serum insulin and c-peptide levels. The patient was discharged from hospital forty-five days after admission.

Imaging at six weeks post Lutetium-177 octreotate therapy showed reduction in size of hepatic metastases. Six cycles of 14 days of capecitabine 1.5g x2/day, followed by 5 days of temozolomide 400mg daily were administered over 5 months. Further tumour regression was seen subsequently (Figure 2). Everolimus, somatostatin analogues and glucocorticoids were discontinued at 3 months post discharge. At 10 months post discharge, the patient has had no recurrence of hypoglycaemia even with strenuous exercise.

**Case 2.**
A 67 year old man presented with biliary obstruction due to a pancreatic mass, with proximity to the superior mesenteric vein preventing surgical resection. Following failure of a biliary stent, a bypass procedure was undertaken. Pathology demonstrated a well-differentiated neuroendocrine tumour in the pancreas with a metastatic deposit in the gastroduodenal node. Indium-111 octreotide scintigraphy demonstrated uptake in the pancreatic mass without evidence of peripheral metastases. There was no hypoglycaemia, nor evidence of multiple endocrine neoplasia type 1, and no further therapy was offered at that time. The patient was then lost to follow up.

Five years later, the patient presented with hypoglycaemia. CT imaging demonstrated hepatic metastases. Despite treatment with prednisolone (up to 60mg daily) and octreotide 100µg x2/day later changed to Sandostatin LAR® (Novartis) 20mg monthly, the patient required frequent meals (as often as 2 hourly overnight) to maintain normoglycaemia. Diazoxide was both ineffective and poorly tolerated. Progression of hypoglycaemia resulted in hospitalisation for intravenous 25% dextrose infusion. He was entered into a Phase IIa trial of capecitabine (2g in the morning and 1.5g in the evening) with Lutetium-177 octreotate. Glycaemic control improved rapidly and intravenous dextrose was safely ceased within 24 hours of Lutetium-177 octreotate administration. All supportive therapies were discontinued over three months with maintenance of normoglycaemia on a normal diet. Four cycles of 7.8GBq Lutetium-177 octreotate and capecitabine were administered over an 8 month period. Reduction in size of hepatic metastases was seen on imaging and post-treatment scintigraphy (Figure 3). Chromogranin A levels reached a nadir of 81 U/L at nine months after initial Lutetium-177 octreotate therapy, from a peak of >800U/L at diagnosis (reference range <18).
Two years after initial radiopeptide therapy, recurrence of hypoglycaemia required further admission for continuous intravenous dextrose. Repeat administration of an identical activity of Lutetium-177 octreotate was commenced, with immediate glycaemic improvement. Unfortunately, post-treatment scintigraphy identified progressive disease. Chemotherapy with capecitabine and temozolomide is under consideration in view of progressive disease burden and high risk for further hypoglycaemia.

DISCUSSION.

These two cases demonstrate the difficulty of controlling hypoglycaemia in patients with inoperable functional malignant insulinoma. In these patients, conventional hyperglycaemic agents lacked efficacy and potentially life-threatening hypoglycaemia necessitated inpatient intravenous dextrose infusion. Novel medical therapies proved successful in amelioration of hypoglycaemia. A review of potential therapies in this context is presented below, with a summary of therapies utilised in our patients presented in Table 3.

Somatostatin Analogues.

Somatostatin is an inhibitor of pancreatic insulin and glucagon release mediated through G-protein transmembrane receptors [3]. Synthetic analogues, such as octreotide, have affinity for sst2A and sst5 receptors and have been used for glycaemic support in insulinoma patients.

Short term (<6 months) use of octreotide at a mean final dose of 621 µg/day (range 50-2000 µg/day) abolished hypoglycaemia in 12 of 16 patients with endogenous hyperinsulinaemia mostly due to insulinoma [4]. In the same trial, all 11
patients who proceeded to longer term use (mean duration 67 months) of octreotide had ongoing benefit with similar doses. However, only one of the four patients with malignant insulinoma treated with octreotide achieved glycaemic control. Octreotide may be less effective, or require higher doses, in malignant compared to benign insulinomas.

Four case reports have shown that Sandostatin LAR® 10-20mg monthly can improve fasting blood glucose and serum insulin in both benign and metastatic malignant insulinoma for up to 3 years [5]. However, a separate report described a patient with malignant insulinoma and hepatic metastases who failed to respond to fortnightly lanreotide 30mg [6]. Pasireotide (SOM-230), a new long acting somatostatin analogue with high affinity for almost all somatostatin receptors except sst4 [7], might have a future role in this area.

Octreotide may additionally have tumour stabilising effects. In patients with metastatic, well-differentiated functioning midgut neuroendocrine tumours, Sandostatin LAR® 30mg monthly increased median time to tumour progression compared to placebo (10.35 versus 5.45 months) [8]. However this study was predominantly in patients with carcinoid tumour.

Predicting therapeutic success for somatostatin analogues remains difficult. Octreotide test doses were unhelpful in malignant insulinoma, and Indium-111 octreotide scintigraphy was also inconsistent at predicting response [4]. However, identifying specific sst2A receptor expression may be helpful [3].

The glycaemic efficacy of somatostatin analogues in malignant insulinoma therefore remains uncertain due to limited published evidence and variable outcomes. Nevertheless, with the knowledge it is both well tolerated [4,8] and may have tumour
stabilising effects, a trial of octreotide seems reasonable for all patients. High doses may be required.

**Radiolabelled somatostatin analogues**

Radiolabelled somatostatin analogue therapy is a novel treatment for inoperable neuroendocrine tumours. \([\text{DOTA}^0,\text{Tyr}^3]\) octreotide has a 9 times higher affinity for sst2 receptors than \([\text{DOTA}^0,\text{Tyr}^3]\) octreotide with high tumour uptake. With respect to radionucleotides, tumour uptake of radioactivity is up to 3-4 times higher after administration of Lutetium-177 octreotate compared with Indium-111 octreotide despite similar renal uptake. Indium-111 also has short tissue penetration making it suboptimal for radiopeptide therapy [9]. Yttrium-90 octreotide has also been studied with at least partial response in 7-33% [7,9]. To maximise radiopeptide uptake, it is necessary to discontinue short acting somatostatin analogues 1 day before treatment, and longer acting analogues 6 weeks prior [9].

In a Dutch study [9], 59 of 131 patients (47%) with inoperable gastroenteropancreatic neuroendocrine tumours (mostly carcinoid) had at least minor response in tumour size and 44 (33%) had stable disease over 16 months median follow up, when treated with Lutetium-177 octreotate (cumulative activity of 27.8 to 29.6 GBq). Predictors of remission included Indium-111 octreotide uptake on scintigraphy and low number of hepatic metastases. There was no description of effect on symptoms due to hormone secretion.

Adverse events included minor gastrointestinal symptoms, transient bone marrow toxicity (particularly in patients aged>70 years, but much less frequently than with Indium-111 or Yttrium-90 labelled peptides) and transient male primary hypogonadism. Hypopituitarism due to potential Lutetium-177 octreotate uptake by
the pituitary was not seen. Severe renal impairment occurred in two patients. A large burden of hepatic disease, and lower hepatic reserve, is associated with a higher risk of hepatic failure from Lutetium-177 octreotate, Indium-111 [DTPA0] octreotide or Yttrium-90 [DOTA0,Tyr3] octreotide therapy [9]. In seven patients treated concurrently with capecitabine, there was one case each of severe anaemia, thrombocytopenia, and mild stomatitis [10].

In our two patients, glycaemic response occurred within hours of octreotate administration, persisting in Case 1 for <24 hours, but contributing to complete abolition of hypoglycaemia for 2 years in Case 2. Hence, Lutetium-177 octreotate proved useful in achieving and maintaining euglycaemia after failure of other supportive therapies. The benefits are probably due to a combination of somatostatin receptor activation in the early phase with later anti-tumour effect. No adverse effects were reported by our two patients who had intact hepatic function despite hepatic metastases. Lutetium-177 octreotate may also have potential for treatment of recurrent disease, as demonstrated in our second case.

**mTOR receptor inhibitors – Rapamycin (Sirolimus) and Everolimus.**

Rapamycin (sirolimus), or its derivative everolimus, are mTOR receptor antagonists used to prevent organ transplant rejection and cellular proliferation in drug-eluting coronary stents. These agents cause hyperglycaemia through complex mechanisms inducing hepatic and peripheral resistance to insulin and beta islet cell toxicity [11].

A case series has described four patients with metastatic insulinoma on multiple hyperglycaemic agents who were able to cease, or significantly reduce, other glycaemic supports after introduction of everolimus. Two patients had evidence of
regression in size of tumours [12]. Successful use of sirolimus (rapamycin) 2mg daily for glycaemic support in an elderly man with metastatic insulinoma has also been reported, allowing withdrawal of diazoxide, octreotide and intravenous dextrose [13].

mTOR is a key intracellular component of signalling pathways responsible for cell survival, growth and angiogenesis. [12,13,14,15]. Dysregulation of upstream components can upregulate mTOR, making it a potential target for anti-tumour therapy [14]. A recent open label phase II study demonstrated that everolimus 10mg daily has radiological antitumour effect in patients with progressive metastatic pancreatic neuroendocrine tumours despite chemotherapy [16]. Concurrent mTOR inhibition with long acting depot octreotide is also under investigation [15]. One of our patients received both everolimus and Lutetium-177 octreotate with tumour regression and glycaemic improvement.

mTOR inhibitors are associated with a variety of adverse effects. In a Phase I dose escalation study in cancer patients, dose limitation due to stomatitis and fatigue occurred at 50 mg/week and hyperglycaemia at 10 mg/day [14]. In a Phase II study in low grade neuroendocrine tumours, use of everolimus 5mg daily with long acting depot octreotide was well tolerated with mild apthous ulceration being the most common toxicity of everolimus [15]. When used for cardiac transplantation, the most common adverse effects were fluid retention and infection [17].

Our experience with everolimus suggests efficacy after failure of conventional therapy. Early use of mTOR inhibition in hypoglycaemia refractory to conventional therapy could be considered, but there is no current published experience for use as a first line agent.

*Diazoxide.*
Diazoxide is an antihypertensive benzothiadiazine derivative [18] without diuretic activity, but capable of inducing hyperglycaemia. Potential glycaemic mechanisms include suppression of glucose and adrenergic mediated insulin release [19], or increasing hepatic gluconeogenesis and reducing glucose uptake by cells [20].

Early case series found over 50% achieved amelioration of hypoglycaemia [21] and higher response rates have been described with efficacy reported even after use for over 10 years [18,22]. Although doses as high as 1500mg/day have been reported [18], usually 200-600mg/day orally is used in divided doses. While patients with malignant insulinoma were included in these studies, their outcomes were not separately reported from benign insulinomas.

Adverse effects are common. Fluid retention may be controlled with thiazide diuretics which may also accentuate the hyperglycaemic effects of diazoxide [21,22,23]. Rare, but severe complications include myelosuppression and cardiomyopathy. Stevens-Johnson syndrome has also been described [18].

In our patients, diazoxide was either ineffective at controlling hyperglycaemia or not tolerated. Despite our experience, existing literature supports use of diazoxide as a first-line agent in inoperable functional insulinomas, albeit without specific information for malignant disease.

Glucocorticoids.

Glucocorticoids induce hyperglycaemia through both inhibition of insulin production and increasing peripheral insulin resistance [24]. An early review yielded poor results with only one third of insulinoma patients achieving symptomatic control [21]. Little is published with regard to malignant insulinomas. Novotny et al [6] reported a case with metastatic insulinoma where hypoglycaemia responded to
prednisone (peak dose 60mg/day) despite failure of chemotherapy, radiotherapy, interferon alpha 2b and lanreotide. Our patients did not derive clear benefit from prednisolone therapy at doses up to 60mg orally per day. The use of glucocorticoids for chronic glycaemic support should be balanced against adverse effects.

*Chemotherapy and Biologic Anti-Tumour Therapy.*

Conventional chemotherapy for well differentiated pancreatic neuroendocrine tumours consists of streptozocin in combination with doxorubicin or 5-fluorouracil (5-FU). Combination therapy response rates are highest with streptozocin-doxorubicin (69%) compared with streptozocin-5-FU (35-63%). However, median survival remained poor (up to 2.2 years). Poorly differentiated tumours and carcinoids have lower response rates [7].

Capecitabine, an oral agent which is metabolised to 5-FU, has shown promising results when used in combination with temozolomide. In 17 patients with metastatic pancreatic neuroendocrine tumours refractory to octreotide, 1 had complete pathological response, while 9 achieved partial response on RECIST criteria lasting a median of 284 days [25]. Capecitabine may also act as a radiosensitising agent prior to Lutetium-177 octreotate therapy [26]. No published trials have directly compared streptozocin based chemotherapy and capecitabine-temozolomide or capecitabine-radiopeptide therapy for insulinomas.

Interferon-alpha is a biological agent with anti-tumour effect. It has direct action on cell cycling and angiogenesis, and also modulates immune responses [7]. While more extensively studied in carcinoid tumours, recombinant interferon alpha-2b achieved biochemical response in 29 of 57 patients (median duration of response 20 months) who had malignant pancreatic neuroendocrine tumour when used either as
first-line therapy or post chemotherapy [27]. In the treatment of metastatic carcinoid tumours, interferon-alpha can be safely coadministered with somatostatin analogues, but it is unclear if there are any additive benefits [7]. Concurrent streptozocin based combination chemotherapy with interferon alpha had significant adverse effects without additional benefit [7].

Chemotherapy with capecitabine and temozolomide was commenced in case 1 due to extensive disease precluding invasive options and ongoing refractory symptoms, while in case 2 it was utilised as part of a trial protocol. While reasonable response rates can be achieved with chemotherapy and there has been evidence of symptomatic improvement in functioning carcinoids, potential adverse effects would prevent use as a first-line agent for glycaemic control.

*Invasive Therapies.*

Reduction in hepatic metastatic tumour burden to control symptoms was not feasible in our two patients, but remains an important option. Surgical resection can be considered if more than 90% of hepatic disease can be removed [28]. Other techniques include arterial embolisation with or without local chemotherapy and ablation with radiofrequency or cryotherapy [7,29]. Chemoembolisation may achieve symptomatic and biochemical control in metastatic neuroendocrine tumours [7], with reported mortality of around 2-5% [29]. Concurrent somatostatin analogue therapy can prevent hormonal crises. Post embolisation syndrome (nausea, fever, tachycardia, abdominal pain, elevated transaminases) is the most common adverse event [7]. Another invasive option, hepatic transplantation, has been associated with poor survival [29].
CONCLUSION.

In the cases we have presented, conventional medical therapies for glycaemic control in unresectable malignant insulinoma were unsuccessful. Despite prednisolone, diazoxide and octreotide treatment, recurrent hypoglycaemia persisted and required frequent enteral feeding and intravenous dextrose infusion. The availability of new methods of combating hypoglycaemia enabled us to maintain a good quality of life in these two patients.

Hypoglycaemia due to malignant insulinoma is less responsive to diazoxide, prednisolone and octreotide than in benign disease. But, until improved clinical evidence becomes available, conventional therapies still have an initial role. Consideration should be given to earlier use of novel therapies for refractory hypoglycaemia in unresectable disease. mTOR inhibition can be an effective option in this situation, with local availability of specialised therapies (such as chemoembolisation or radiopeptide therapy) determining their utility. Chemotherapy or interferon-alpha can be considered after failure of other modalities. We have shown the effectiveness of Lutetium-177 octreotide and mTOR inhibition. Further research is required to determine their role in the treatment of functional malignant insulinoma.

DECLARATION OF INTERESTS AND STATEMENT REGARDING FUNDING.

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.
REFERENCES


Figure 1.
Figure 2. T2 weighted MRI with gadolinium for Case 1. There are numerous hepatic metastases at diagnosis (left image). Seven months after therapy with Lutetium-177 labelled Octreotate, there is regression in the size and number of hepatic metastases (right image). Six cycles of systemic chemotherapy had also been administered by this time. The diameter of the primary pancreatic tail lesion had regressed by 17%, with 20-50% reduction in diameter of larger hepatic metastases and near-iso signal appearance of smaller innumerable hepatic metastases on portal venous and delayed studies.

60x30mm (600 x 600 DPI)
Table 1. Characteristics of Cases at onset of Hypoglycaemia. Reference ranges for biochemical data are included in parentheses. Plasma C-peptide and insulin levels given below occurred at the time of the plasma glucose nadir.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Plasma Glucose nadir (mmol/L)</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>C-peptide at time of glucose nadir (nmol/L)</td>
<td>3.7 (0.2-0.9)</td>
<td>2.2 (0.2-0.9)</td>
</tr>
<tr>
<td>Insulin at time of glucose nadir (mU/L)</td>
<td>91 (&lt;12)</td>
<td>95(&lt;12)</td>
</tr>
<tr>
<td>Chromogranin A (IU/L)</td>
<td>&gt; 800 (&lt;18)</td>
<td>&gt; 800 (&lt;18)</td>
</tr>
</tbody>
</table>
Table 2. Complications potentially attributable to use of Everolimus in Case 1.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Potentially confounding factors</th>
<th>Time to onset after everolimus commenced</th>
<th>Management</th>
<th>Time until resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Retention.</td>
<td>Intravenous dextrose, prednisolone, diazoxide.</td>
<td>1 day.</td>
<td>Spironolactone up to 100mg/day.</td>
<td>7 days to achieve stable weight without peripheral pitting oedema.</td>
</tr>
<tr>
<td>Leukopaenia (nadir of 3.12 x 10⁹ /L, reference 4-11 x 10⁹ /L)*.</td>
<td>Nil.</td>
<td>Decline in white cell count evident after 1 day, with nadir at 10 days post commencement.</td>
<td>Nil.</td>
<td>Returned to normal reference levels within 10 days after nadir reached.</td>
</tr>
<tr>
<td>Herpes simplex virus-1 folliculitis of the neck.</td>
<td>Prednisolone.</td>
<td>2 days.</td>
<td>Chlorhexidine wash, no specific anti-viral therapy.</td>
<td>Complete resolution within 14 days.</td>
</tr>
</tbody>
</table>

* Consisting of lymphopaenia (nadir 1.03 x 10⁹ /L, reference 1.2-4 x 10⁹ /L) and neutropaenia (nadir 1.57 x 10⁹ /L, reference 2-7.5 x 10⁹ /L).
Table 3. Summary of dose ranges, time to onset of glycaemic action and major adverse effects for agents utilised in our two patients as described in published literature or observed in our cases.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose ranges</th>
<th>Onset of glycaemic action</th>
<th>Common or Major Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin Analogues.</td>
<td>Octreotide 50-3000mcg/day s/c as 2-3 divided doses or continuous infusion.</td>
<td>Hours, but may not be as effective in malignant insulinoma as benign [4]</td>
<td>Gastrointestinal including cholestasis with gallstones [4] and steatorrhoea with malabsorption [30], marrow suppression [8], risk of hypoglycaemia due to suppression of counterregulatory hormones [31].</td>
</tr>
<tr>
<td></td>
<td>Up to 14-20 days [5]</td>
<td></td>
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<tr>
<td></td>
<td>Sandostatin LAR® 10-30mg per month has glycaemic and possible anti-tumour effect [5, 8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td>For glycaemic support (no antitumour effect): Up to 1500mg/day (adult) [18], but most common dose was 100mg x3/day in UK</td>
<td>&lt;1 week [23]</td>
<td>Fluid retention and weight gain amenable to thiazides, hirsutism, gastrointestinal (nausea) [18,22], Stevens-Johnson Syndrome (single case) [18]. Myelosuppression and cardiomyopathy are rare.</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>Drug/Procedure</td>
<td>Duration</td>
<td>Side Effects</td>
</tr>
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<td>----------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Glucocorticoids</td>
<td>Maximum dose of prednisone 60mg/day [6].</td>
<td>&lt;1 week</td>
<td>Skin, muscle atrophy, osteoporosis, glaucoma and cataracts, altered mood, psychosis, adrenal atrophy, dyslipidaemia, fluid retention, hypertension, increased cardiovascular risk, immunosuppression, gastrointestinal (ulcer, pancreatitis, bleeding) [24]</td>
</tr>
<tr>
<td>mTOR inhibition</td>
<td>Everolimus 5-10mg/day [15,16]</td>
<td>From our experience &lt;2 weeks.</td>
<td>Immunosuppression, marrow suppression, skin rash, angular stomatitis, pneumonitis, dyslipidaemia, hepatotoxicity, nephrotoxicity, electrolyte abnormalities [14], fluid retention [17].</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Capecitabine-Temozolomide</td>
<td>Unknown</td>
<td>Thrombocytopenia, one case of hand-foot syndrome. Only Grade III toxicities were listed in this abstract [25].</td>
</tr>
<tr>
<td>Radiolabelled somatostatin analogues</td>
<td>Lutetium-177 octreotate with or without capecitabine.</td>
<td>Hours</td>
<td>Nausea, vomiting, abdominal pain particularly if hepatomegaly, nephrotoxicity, hepatotoxicity particularly if reduced hepatic reserve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(somatostatin agonist),</td>
<td></td>
</tr>
<tr>
<td>weeks to months (anti-tumour)</td>
<td>from metastatic disease, transient primary hypogonadism (male) [9]. When used concurrently with capecitabine, mild stomatitis, WHO grade 3 anaemia and thrombocytopaenia were noted [10].</td>
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