Systemic Anti Cancer Therapy Protocol

Streptozocin and Doxorubicin Advanced Pancreatic Neuroendocrine Tumours (NETs)

PROTOCOL REF: MPHASTDOGA
(Version No: 1.0)

Approved for use in:

Treatment of inoperable, advanced or metastatic well-differentiated grade 1-2 pancreatic NETs.

Dosage:

Drug	Dose	Route	Frequency
Streptozocin	**500 mg/m^2**	IV infusion	Days 1 to 5 of a 42 day cycle
Doxorubicin	**50 mg/m^2**	IV Bolus	Days 1 and 22 of a 42 day cycle

For up to 4 cycles**

****May be repeated until disease progression or unacceptable toxicity up to a maximum lifetime doxorubicin dose of 500mg / m^2**

Administration:

Streptozocin only has a 24 hour shelf life once reconstituted therefore cycles should be scheduled to start on a Monday as pharmacy is unable to produce Streptozocin at weekends.

Emetogenic risk:

Highly emetogenic.

Supportive treatments:

Aprepitant 125mg one hour before chemo, 80mg once a day on days 2 and 3

Dexamethasone 4mg twice a day for 3 days (day 6 onwards)

Domperidone 10mg three times a day when required

Ondansetron 8mg twice a day when required

Extravasation risk:

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

Streptozocin: VESICANT

Doxorubicin: VESICANT

Dosing in renal and hepatic impairment:

Renal	Streptozocin	• CrCl 46 -60ml/min – 50% dose • CrCl 31-45ml/min – not recommended, if unavoidable reduce to 25% dose • CrCl ≤ 30ml/min– contra-indicated
	Doxorubicin	Consider dose reducing by 25% if CrCl < 10ml/min

Hepatic	Streptozocin	No dose adjustment necessary
	Doxorubicin	• Bilirubin 20-50 µmol/l – 50% dose • Bilirubin 51 – 86 µmol/l – 25% dose • Bilirubin > 86 µmol/l or Child-Pugh C – not recommended

Interactions:

Live and live-attenuated vaccines- Concomitant use is contraindicated as may induce fatal generalised vaccinal disease.

Nephrotoxic drugs – can increase the risk of nephrotoxicity with streptozocin therefore concomitant use should be avoided (e.g. aminoglycosides such as gentamicin).

Cardiac drugs – careful cardiac monitoring is required when drugs affecting cardiac function (such as calcium channel blockers) due to risk of cardiotoxicity with doxorubicin.

Phenytoin – decreases cytotoxic effect of streptozocin on beta cells of pancreas therefore concomitant use should be avoided. Doxorubicin may reduce phenytoin plasma levels.

Treatment schedule:

Days 1 to 5 to be given as inpatient and Day 22 to be given as outpatient

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	60 mins before chemotherapy
	Sodium Chloride 0.9% 1000mL		**IV**	Over 60mins
	Ondansetron	**8mg**	**IV**	30 mins before chemotherapy
	Dexamethasone	**9.9mg**	**IV**	30 mins before chemotherapy
	Streptozocin	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500ml over 120 minutes
	Doxorubicin	**50mg/m^2**	**IV**	Over 15 minutes Concurrent administration, doxorubicin at 400ml/hr and sodium chloride 0.9% at 100ml/hr
2	**Aprepitant**	**80mg**	**IV**	30 mins before chemotherapy
	Sodium Chloride 0.9% 1000mL		**IV**	Over 60mins
	Ondansetron	**8mg**	**IV**	30 mins before chemotherapy
	Dexamethasone	**9.9mg**	**IV**	30 mins before chemotherapy
	Streptozocin	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500ml over 120 minutes
3	**Aprepitant**	**80mg**	**IV**	30 mins before chemotherapy
	Sodium Chloride 0.9% 1000mL		**IV**	Over 60mins
	Ondansetron	**8mg**	**IV**	30 mins before chemotherapy
	Dexamethasone	**9.9mg**	**IV**	30 mins before chemotherapy
	Streptozocin	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500ml over 120 minutes
4	**Ondansetron**	**8mg**	**IV**	30 mins before chemotherapy
	Sodium Chloride 0.9% 1000mL		**IV**	Over 60mins
	Dexamethasone	**9.9mg**	**IV**	30 mins before chemotherapy
	Streptozocin	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500ml over 120 minutes
5	**Ondansetron**	**8mg**	**IV**	30 mins before chemotherapy
	Sodium Chloride 0.9% 1000mL		**IV**	Over 60mins
	Dexamethasone	**9.9mg**	**IV**	30 mins before chemotherapy
	Streptozocin	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500ml over 120 minutes
22	**Dexamethasone**	**9.9mg**	**IV**	30 mins before chemotherapy
	Doxorubicin	**50mg/m^2**	**IV**	Over 15 minutes Concurrent administration, doxorubicin at 400ml/hr and sodium chloride 0.9% at 100ml/hr

Main toxicities:

- Nausea and vomiting
- Diarrhoea
- Mucositis
- Anorexia
- Alopecia
- Phlebitis
- Cardiotoxicity*
- Renal toxicity
- Raised liver transaminases
- Hyperglycaemia
- Anaemia
- Thrombocytopenia
- Neutropenia

*****Cardiotoxicity may manifest as dyspnea, tachycardia, ECG changes and decrease in LVEF

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D22	Cycle 2 D1	Cycle 2 D22	Cycle 3 D1	Cycle 3 D22	Ongoing
Informed Consent	X							
Clinical Assessment	X	X		X		X		Every cycle
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
Bone Profile	X	X	X	X	X	X	X	Every Cycle
Serum Creatinine and eGFR (MDRD formula)	X	X	X	X	X	X	X	Every cycle
Urinalysis (check for proteinuria)	X							2-4 weeks after last dose of streptozocin (to be checked by clinical team) and if clinically indicated
Random blood glucose	X	X	X	X	X	X	X	Repeat if clinically indicated
CT scan	X					X		Every 12 weeks unless clinically indicated
ECG	X							Repeat if clinically indicated
Baseline ECHO or MUGA	X							If clinically indicated
Blood pressure measurement	X							Repeat if clinically indicated
Respiratory Rate	X							Repeat if clinically indicated
Weight	X	X	X	X	X	X	X	Every cycle
Height	X							

Dose Modifications and Toxicity Management:

Appearance	Streptozocin Dose	Doxorubicin Dose
1st	80%	100%
2nd	80%	80%
3rd	60%	80%

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Proceed on day 22 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Omit on day 22 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 74 x 10^9/L

On day 22 of the cycle if blood results do not meet the above levels the patient will miss that dose and proceed to the next cycle.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

References:

1. Summary of Product Characteristics: Zanosar 1g, powder for concentrate for solution for infusion. Intrapharm Laboratories Limited. Last updated: 26/02/2019. Available via: https://www.medicines.org.uk/emc

2. Summary of Product Characteristics: Doxorubicin 2mg/ml concentrate for solution for infusion. Seacross Pharmaceuticals Limited. Last review: 11/02/2016. Available via: https://www.medicines.org.uk/emc
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
4. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG Klaassen D. Streptozocin–doxorubicin, streptozocin–fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519–523.
5. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.