Systemic Anti Cancer Treatment Protocol

Trabectedin
Sarcoma

PROTOCOL REF: MPHATRABE
(Version No: 1.2)

This protocol has been temporarily amended - please see the SRG Guidelines during COVID-19 Sarcoma Cancer

Approved for use in:

Soft tissue sarcoma (NICE TA 185) - Particularly useful for myxoid liposarcomas, leiomyosarcomas and synovials.

Advanced disease

Desmoplastic small round cell tumour

After doxorubicin and ifosfamide

If doxorubicin and ifosfamide are unsuitable or intolerance occurs

PS 0-2

Dosage:

Drug	Dosage	Route	Frequency
Trabectedin	1.5mg/m^2	IV	Every 21 days

Supportive treatments:

Anti-emetic potential - Low

Dexamethasone IV 20mg prior to trabectedin

Domperidone 10mg oral tablets, up to 3 times a day or as required

Extravasation risk:

High – necrotic and may require debridement. No specific antidote

Administration:

Ensure that Medical Assessment for this cycle has been completed and check that treatment has been approved **before** any administration of trabectedin.

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	20mg	IV	30 minutes before trabectedin
1	**Trabectedin**	**1.5mg / m^2**	**IV**	In 1000mL Sodium Chloride 0.9% over 24 hours

Or

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone	20mg	IV	30 minutes before trabectedin
1	**Trabectedin**	**1.5mg / m^2**	**IV**	In infusion device over 24 hours

Give until clinical or radiological evidence of disease progression or unacceptable toxicity.

Notes:

Administration through a central line strongly recommended

Avoid administration with potent inhibitors of CYP3A4 if possible. This includes clarithromycin, aprepitant, fluconazole and ketoconazole. If not possible monitor closely and consider dose reductions. Inducers of CYP3A4 e.g. St John's Wort, rifampicin and phenobarbital may reduce exposure to trabectedin.

Concurrent administration with phenytoin may reduce phenytoin levels

Criteria for each cycle to proceed:

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

For ANC 1.0 to 1.5 x 10^9/L – discuss with consultant.

Defer treatment for one week. If haematological toxicity not recovered at this point then discuss with consultant.

Bilirubin	Less than upper limit of normal (ULN)
Alkaline Phosphatase	Less than 2.5 times ULN
Albumin	Above 25g/L
ALT and AST	Less than 2.5 times ULN
Creatinine clearance	Above 30mL/min
Creatine phosphokinase (CPK)	Less than 2.5 times ULN
Haemoglobin	Above 90 g/L

Main Toxicities:

Myelosuppression (may be life threatening), nausea and vomiting, lethargy, alopecia, bruising bleeding, myalgia, rhabdomyolysis (see below), sore mouth, hypotension, dyspnoea cough, peripheral oedema, constipation, diarrhoea, anorexia, headache, impaired fertility

Investigations and treatment plan:

	Pre	Cycle 1*	Cycle 1 day 8 and day 15	Cycle 2	Cycle 2 day 8 and day 15	Cycle 3	Cycle 4	Comments / ongoing
Medical Assessment	X			X		X		Day 1 of each cycle before treatment
Nursing Assessment	X	X		X		X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	Every cycle
AST	X	X	X	X	X	X	X	Every cycle
Creatine Kinase (CK)	X	X	X	X	X	X	X	Weekly for 6 weeks then with each cycle
CT scan	X					X		After cycle 3 then as clinically indicated
Informed Consent	X							
Blood pressure measurement	X							Repeat if clinically indicated
PS recorded	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	Every cycle
Weight recorded	x	x	x	x	x	x	x	Every cycle

LFTs to include AST, ALT, bilirubin and Alk Phos

Arrange for day 8 and day 15 blood results to be reviewed

Dose Modifications and Toxicity Management:

Haematological toxicity

If any of these occur during the cycle reduce the next dose by one dose level as shown in the table below:

ANC < 0.5 x 10^9/L lasting more than 5 days or associated with fever or infection

Platelets < 25 x 10^9/L

Increase of bilirubin > ULN and/or alkaline phosphatase > 2.5 ULN

Increase of AST / ALT > 2.5 ULN not recovered by day 21

Any grade other 3 / 4 toxicity or adverse reaction

	Trabectedin dose
Starting dose	1.5 mg/m^2
First reduction	1.2 mg/m^2
Second reduction	1 mg/m^2

Retreatment may be delayed up to 3 weeks to allow recovery and to meet the haematological and non-haematological criteria for continued treatment.

Once the dose has been reduced, do not increase for subsequent cycles

Non-haematological toxicity

<table>
<tr><td>Renal</td><td><table><tr><td>CrCl ≥ 30mL/min</td><td>Treat at the current dose level</td></tr><tr><td>CrCl < 30mL/min</td><td>Refer to consultant</td></tr></table></td></tr>
<tr><td>Hepatic</td><td>See above, note that if rises in alk phos may be considered osseus in nature use GGT or hepatic enzyme 5-nucleotidase</td></tr>
<tr><td>Rhabdomyolysis</td><td>This has been rarely reported but usually occurs in conjunction with myelotoxicity, severe liver function abnormalities and / or renal failure. Monitor CK closely in any patients experiencing these toxicities or in any patients reporting muscle pain.

Report any grade 3 CK toxicity to Consultant as soon as possible.</td></tr>
<tr><td>Other grade 3 / 4 toxicity</td><td>Delay until recovery and reduce trabectedin dose as shown in the table above</td></tr>
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References:

Electronic Medicines Compendium, Yondelis®, https://www.medicines.org.uk

Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol. 2009;27(25):4188-96.