Trabectedin

Indication

Treatment of advanced soft tissue sarcoma in patients who have failed, or are intolerant of/unsuitable for, treatment with anthracyclines and ifosfamide.

For patients with WHO performance status 0-2.

There is a patient access scheme associated with this treatment. Once a patient has received 5 cycles of treatment the manufacturer provides the sixth and subsequent treatments free of charge.

(NICE TA185)

ICD-10 codes

Codes with a pre-fix C49

Regimen details

Day	Drug	Dose	Route
1	Trabectedin	1.5mg/m^2	IV infusion

Cycle frequency

21 days.
May extend to 28 days if neutrophils slow to recover, or WHO performance status rises, or quality of life affected.

Number of cycles

Continued until disease progression or intolerable toxicity.

Administration

Trabectedin is administered in sodium chloride 0.9% or glucose 5% over 24 hours. It is strongly recommended that it is administered via a central venous line. Trabectedin may be administered using an ambulatory infusion device. The concentration of the infusion should be ≤ 0.03mg/mL.

Trabectedin may, if there is no central venous line be administered via a peripheral line in an infusion bag ≥ 1000mL.

Pre-medication

Patients must receive corticosteroids as a pre-medication. Dexamethasone 20mg IV STAT, 30 minutes before administration is recommended. In addition to its antiemetic effect, this also has a hepato-protective effect. Additional anti-emetics may also be required as per local policy.

Emetogenicity

This regimen has moderate emetogenic potential.

Additional supportive medication

Antiemetics as per local policy.
H_2 antagonist or proton-pump inhibitor if required.
Dexamethasone 4mg BD is recommended the day before treatment and on days 2 and 3.
GCSF may be considered, as per local policy

Extravasation

Trabectedin is vesicant (Group 5)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Creatine phosphokinase (CPK)	14 days

Consider echocardiogram to assess LVEF – baseline and periodically as clinically indicated

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for the first 2 cycles, then within 96 hours of each subsequent cycle
U+Es (including creatinine)	Weekly for the first 2 cycles, then within 96 hours of each subsequent cycle
LFTs	Weekly for the first 2 cycles, then within 96 hours of each subsequent cycle
Creatine phosphokinase (CPK)	Weekly for the first 2 cycles, then within 96 hours of each subsequent cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Haemoglobin	≥ 9g/dL
Creatinine clearance	≥ 30mL/min
ALT/AST	≤ 2.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Bilirubin	≤ ULN
Albumin	≥ 25g/L
CPK	≤ 2.5 x ULN

Dose modifications

Trabectedin dose reductions occur in a graded manner each time a significant toxicity is encountered as per the following table:

Starting Dose	1.5mg/m^2
First Reduction	1.2mg/m^2
Second Reduction	1.0mg/m^2

Once a dose has been reduced because of toxicity, dose escalation in subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced.

- **Haematological toxicity**

Delay 1 week if neutrophils < 1.5 x 10^9/L or platelets < 100 x 10^9/L. Consider 4-weekly dosing if patient experiences recurrent delays.

If any of the following events occur at any time between cycles, the dose must be reduced one level for subsequent cycles (as per the dosing table above):

- Neutropenia - neutrophils < 0.5 x 10^9/L lasting for more than 5 days, or associated with fever or infection.
- Thrombocytopenia – platelets < 25 x 10^9/L

- **Renal impairment**

No dose modification required for mild to moderate renal impairment.
Trabectedin is not recommended if CrCl< 30mL/min.

- **Hepatic impairment**

If any of the following events occur between cycles, the dose must be reduced one level for subsequent cycles (as per the dosing table above):
- Bilirubin > ULN and/or ALP > 2.5 x ULN
- ALT/AST > 2.5 x ULN which has not recovered by day 21

- **Other toxicities**

Cardiac Dysfunction
Patients should be monitored for clinical cardiac signs or symptoms. Although not routinely necessary, it is also recommended to consider checking LVEF at baseline and periodically during the treatment; particularly in patients at risk of cardiomyopathy from previous anthracycline exposure or in patients with symptoms of decreasing cardiac function. If LVEF below lower limit of normal, trabectedin should be withheld. If no recovery within 3 weeks or symptomatic cardiomyopathy, permanently discontinue treatment.

Rhabdomyolysis
Trabectedin **must not** be used in patients with CPK > 2.5 x ULN. Rhabdomyolysis has been uncommonly reported, usually in association with myelotoxicity, severe liver function test abnormalities and/or renal or multi-organ failure. Therefore, CPK should be closely monitored whenever a patient may be experiencing any of these toxicities or muscle weakness or muscle pain. If rhabdomyolysis occurs, supportive measures such as parenteral hydration, urine alkalinisation and dialysis should be promptly established, as indicated.

For any other grade 3-4 toxicity the dose must be reduced one level for subsequent cycles (as per the dosing table above).

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Rhabdomyolysis (trabectedin must not be administered if CPK > 2.5 x ULN)
Severe hepatic injury

- **Frequently occurring side effects**

Myelosuppression
Raised CPK
Abnormal LFTs
Nausea and vomiting
Diarrhoea
Mucositis
Fatigue
Myalgia and arthralgia

Headache
Alopecia

- **Other side effects**

Poor appetite
Insomnia
Hypotension
Dyspnoea

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (including: ketoconazole, fluconazole, ritonavir, clarithromycin, aprepitant) – may increase trabectedin levels: avoid concomitant use.

CYP3A4 inducers (including: rifampicin, phenobarbital, St John's Wort) – may reduce trabectedin levels: avoid concomitant use.

Phenytoin: may reduce phenytoin absorption leading to convulsions: avoid concomitant use.

Medications which may cause rhabdomyolysis, eg statins: use with caution.

Hepatotoxic drugs should be avoided due to increased risk of hepatotoxicity.

P-gp inhibitors (including cyclosporine, verapamil) – may affect trabectedin distribution and elimination: use with caution.

Alcohol consumption must be avoided due to risk of hepatotoxicity.

Additional comments

Women of childbearing potential must use effective contraception during treatment and for 3 months thereafter, and immediately inform the treating physician if a pregnancy occurs.

Men of fertile age must use effective contraception during treatment and 5 months after treatment.

References

- National Institute of Health and Clinical Excellence Guideline TA185. Accessed 22 July 2015 via www.nice.org.uk
- Summary of Product Characteristics Trabectedin (Pharma Mar) accessed 2 November 2017 via www.medicines.org.uk
- George D. Demetri. Et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy. JCO.2015.62.4734

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