Siltuximab IV (SYLVANT®)

INDICATION

Treatment of adult patients with idiopathic multicentric Castleman's disease (iMCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

Note: This drug regimen requires individual funding request (IFR) approval

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TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and MDT approval sought
2. Rule out active infection and Haemoglobin level should be < 17g/l. Patients should receive pneumococcal vaccination and annual flu vaccination.
3. Record stage of disease - CT scan (neck, chest, abdomen and pelvis) and / or PET-CT, presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine.
4. Blood tests - FBC, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Triglycerides, Igs, β2 microglobulin, LDH, Hep B&C, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
5. Send a "group and save" sample to transfusion.
6. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy.
7. ECG +/- Echo - if clinically indicated.
8. Record performance status (WHO/ECOG).
9. Record height and weight.
10. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
11. Hydration - in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
12. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Pre-medication (30 minutes prior to Siltuximab infusion)
Chlorphenamine 10mg IV bolus
Paracetamol 1g PO Stat
Hydrocortisone 100mg IV bolus

SILTUXIMAB 11 mg/kg in 250mL Glucose 5% iv infusion over 1 hour via an infusion set equipped with a 0.2 µm in-line filter.

CYCLE FREQUENCY

Repeat every 3 weeks until treatment failure. Consider decreasing frequency if disease stable
Note: Ensure IFR funding covers the treatment duration and number of cycles prescribed.

RESTAGING

Response should be monitored using a CT scan Chest/ Abdomen/ Pelvis, CRP, fibrinogen and VEGF levels after 4 cycles of treatment. Improvement in B symptoms and fall in inflammatory markers are also markers of response.

Subsequent review using blood markers (CRP, fibrinogen and VEGF levels) should be performed at least 3 monthly

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients
Patients less than 18 years of age
Pregnancy and lactation: Siltuximab is not recommended during pregnancy and in women of childbearing potential not using contraception. Siltuximab should be given to a pregnant woman only if the benefit clearly outweighs the risk.

DOSE MODIFICATIONS

There are no dose modifications for haematological toxicity. Prior to each cycle, ensure:

- ANC ≥ 1.0 x 10^9/L
- Plt ≥ 50 x 10^9/L
- Hb < 170 g/L *

*Note, Siltuximab may increase haemoglobin levels in MCD patients
Consider delaying treatment until the above parameters are met.

Infusion related reactions and hypersensitivity
In case of mild to moderate infusion reactions, slow or stop infusion. Upon resolution of the reaction, re-initiate the infusion at a lower rate and administer chlorphenamine, , paracetamol , and hydrocortisone . For patients who do not tolerate the infusion following these interventions, Siltuximab should be discontinued.
If the patient develops a severe infusion-related reaction, anaphylaxis, severe allergic reaction, or cytokine release syndrome related to the infusion, further administration of Siltuximab should be discontinued.

Other toxicities:
Withhold treatment in case of severe infection or non-haematological toxicity, and restart at same dose once resolved.

Renal impairment

No formal study of the effect of renal impairment on the pharmacokinetics of siltuximab has been conducted. For patients with baseline calculated creatinine clearance of 12 mL/min or greater, there was no meaningful effect on siltuximab pharmacokinetics (PK). Four patients with severe renal impairment (creatinine clearance 12 to 30 mL/min) were included in the data set.

Hepatic impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of siltuximab has been conducted. For patients with baseline alanine transaminase up to 3.7 times the upper limit of normal baseline albumin ranging from 15 to 58 g/L, and baseline bilirubin ranging from 1.7 to 42.8 mg/dL there was no meaningful effect on siltuximab PK.

INVESTIGATIONS

Bloods – CRP, FBC, Igs, VEGF, IL-6 if available, Triglycerides, fibrinogen prior to every cycle of therapy
CT – Chest Abdomen, Pelvis every 4 cycles first year until response achieved and then dependent on symptoms
U&Es and Creatinine
LFTs

CONCURRENT MEDICATION

Allopurinol in treatment naïve patients/bulky disease.
Consider prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min
Consider prophylactic co-trimoxazole 960mg OD on M/W/F at clinician's discretion
Consider other prophylactic anti-bacterial in selected patients at clinician's discretion

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Extravasation risk: siltuximab-none

EMETIC RISK

Low emetic risk

SPECIAL WARNINGS / PRECAUTIONS (See SPC for details)

Concurrent active infections
Live, attenuated vaccines should not be given concurrently or within 4 weeks before initiating Siltuximab
Patients at increased risk of GI perforation
Women of childbearing potential must use effective contraception during and up to 3 months after treatment

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS (See SPC for details)

Infusion-related reactions and hypersensitivity
Infections (upper respiratory tract) and nasopharyngitis
Neutropenia and thrombocytopenia
Hypertriglyceridaemia
Rise in Haemoglobin levels
Rash
Hypertension
Abdominal pain
Oedema
Weight gain
Renal impairment

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

1. Summary of Product Characteristics Siltuximab (SYLVANT®) last updated Sept 2021.
2. Rhee F.van, et al. Siltuximab for Multicentric Castleman's Disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-74.
3. Rhee F. van, et al. Patient-reported Outcomes for Multicentric Castleman's Disease in a randomised, Placebo-controlled study of Siltuximab. Open access at Springerlink.com (DOI 10.1007/s40271-015-0120-5)

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, concurrent medication section, drug regime, dose modification	May 2016	1.1	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated dose modifications, adverse effects and references	July 2017	1.2	June 2018
Myeloma Protocol Review 2019	Update of general pre-assessment, restaging, investigations, concurrent medicines, extravasation risk and references	June 2019	1.3	June 2020
NSSG Myeloma Group	Annual protocol review 2022, updated: contraindications, other toxicities, renal/hepatic impairment	June 2022	1.4	June 2023