Blinatumomab

Indication

Treatment of Philadelphia-chromosome-negative relapsed or refractory precursor B-cell acute lymphoblastic leukaemia (ALL).

(NICE TA450)

ICD-10 codes

Codes with a prefix C91.1

Regimen details

Cycle 1:

Day	Drug	Dose	Route
1-7	Blinatumomab	9 micrograms/day	Continuous IV infusion
8-28	Blinatumomab	28 micrograms/day	Continuous IV infusion

Subsequent cycles (cycles 2-5):

Day	Drug	Dose	Route
1-28	Blinatumomab	28 micrograms/day	Continuous IV infusion

Cycle frequency

6 week cycles: 28 days of treatment followed by 14 days treatment free interval.

Number of cycles

2 cycles. If patient experiences complete remission after 2 cycles they may have up to 3 additional cycles of consolidation.

Administration

Blinatumomab is administered as a continuous IV infusion. A central venous access line is required.

Blinatumomab should be administered via a polyolefin, PVC non-DEHP, or EVA intravenous infusion line with a low protein-binding 0.2 µm in-line filter. Administer using programmable, lockable and alarmed CADD pumps. Monitor for infusion reactions.

Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.

For all subsequent cycles and for reinitiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.

Treatment should be scheduled to commence in the morning with bag changes also in the mornings. The bag must be changed within 4 hours of the planned time regardless of the volume of infusion fluid remaining in the bag. Note expiry time of 96 hours. When commencing treatment and determining bag change days ensure weekends and bank holidays are considered.

NOTE: Do not flush the infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage.

Medication errors (including underdosing and overdosing) have been observed with blinatumomab. It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimise this risk.

Pre-medication

Dexamethasone 20 mg IV should be administered 1 hour prior to initiation of each infusion (i.e. each cycle).

Regular paracetamol (500mg-1g PO QDS) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle.

Intrathecal chemotherapy prophylaxis is recommended before and during treatment to prevent central nervous system ALL relapse.

Patients should have a fluid intake of at least 3 litres per day.

For patients with high tumour burden consider treatment with pre-phase steroids, such as dexamethasone 10mg/m^2/day (up to a maximum of 24 mg/day).

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Pre medication as above.
Allopurinol 300mg OD (or 100mg OD if creatinine clearance <20mL/min) for the first 1-2 cycles.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiviral, PCP and antifungal prophylaxis as per local policy.

Extravasation

Blinatumomab is neutral

Investigations – pre first cycle

Investigation	Validity period
FBC + coagulation screen	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
LDH	14 days
Glucose	14 days

Other pre-treatment investigations:
Hepatitis B and C, HIV, EBZ, CMV, VZV serology
If clinical suspicion of cardiac dysfunction: ECG and ECHO
Baseline neurological examination

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+Es (including creatinine)	96 hours
LFTs	96 hours

Patients should also be monitored for signs and symptoms of neurologic events. This should include a weekly "writing test" where patient writes a simple sentence in their medical records.

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	> 1.0 x 10^9/L
Platelets	> 100 x 10^9/L
CrCl	> 30mL/min
Bilirubin	See below
ALT/AST	See below

Dose modifications

If treatment is interrupted:

For ≤ 7 days: continue the same cycle to a total of 28 days of infusion including days before and after the interruption in that cycle.
For >7 and ≤ 14 days: start a new cycle
For >14 days: discontinue treatment permanently (see table below for exceptions).

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L discuss with consultant.

- **Renal impairment**

Dose adjustment is not necessary in patients with mild to moderate renal dysfunction. The safety and efficacy of blinatumomab has not been studied in patients with severe renal impairment.

- **Hepatic impairment**

Based on pharmacokinetic analyses, no effect of baseline liver function on blinatumomab exposure is expected and adjustment of the initial dose is not necessary. The safety and efficacy of blinatumomab has not been studied in patients with severe hepatic impairment. See below for management of elevated LFTs during treatment.

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Cytokine release syndrome	Grade 3	Interrupt infusion until resolved. *Recommence at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue permanently.
Neurological toxicity	Grade 3	Interrupt infusion until resolved to ≤ Grade 1 for at least 3 days. *Recommence at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur. When recommencing treatment pre medicate with 24mg dexamethasone (then taper over 4 days). If toxicity occurred at 9 mcg/day or takes >7 days to resolve: discontinue permanently.
	Convulsion	If more than one convulsion occurs: discontinue permanently.
	Grade 4	Discontinue permanently.
Tumour lysis syndrome	Grade 3	Interrupt infusion until resolved. *Recommence at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue permanently
Elevated LFTs (ALT/AST and/or bilirubin)	Grade 3	Interrupt infusion until resolved to ≤ Grade 1 *Recommence at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur.
	Grade 4	Consider discontinuing permanently
Other toxicities	Grade 3	Interrupt infusion until resolved to ≤ Grade 1 *Recommence at 9mcg/day. Escalate to 28mcg/day after 7 days if the toxicity does not recur.
	Grade 4	Consider discontinuing permanently

* for patients < 45kg:
Recommence at 5mcg/m^2/day. Escalate to 15mcg/m^2/day after 7 days if the toxicity does not recur.
Refer to Summary of Product Characteristics for further information.

Infusion related reactions:
Reactions including rash, wheezing, flushing, breathlessness, hypotension, face swelling generally occur within 48 hours after initiating infusion. Delayed onset of infusion reactions or in later cycles have also been reported. Patients should be observed closely for infusion reactions, especially during the initiation of the first and second treatment cycles and treated appropriately. Anti-pyretic use (e.g. paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle. Reactions may be clinically indistinguishable from signs and symptoms of cytokine release syndrome.

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

- **Serious side effects**

Myelosuppression
Cytokine release syndrome
Tumour lysis syndrome
Neurological events*
Infusion related reactions
Progressive multifocal leukoencephalopathy
Infections
Pancreatitis

*Neurologic events following initiation of blinatumomab administration have been observed and include encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The median time from initiation of blinatumomab to onset of a neurologic event was within the first 2 weeks and the majority of events resolved with treatment interruption and in some cases discontinuation.

- **Frequently occurring side effects**

Myelosuppression
Headaches
Tremor
Paraesthesia
Hypotension
Cough
Nausea, vomiting
Hypokalaemia
Peripheral oedema
Constipation, diarrhoea
Abdominal pain

- **Other side effects**

Elevated LFTs
Insomnia
Rash
Back pain

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

No formal drug interaction studies have been performed. Results from an *in vitro* test suggest that blinatumomab did not affect CYP450 enzyme activities.

Initiation of blinatumomab causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as necessary.

Additional comments

Women of childbearing potential have to use effective contraception during and for at least 48 hours, after treatment.

References

- Hagop Kantarjian, M.D, et al. Blinatumomab versus Chemotherapy for Advanced Lymphoblastic Leukemia. N Engl J Med 2017; 376:836-847.
- N Gökbuget. et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016 Sep; 6(9): e473.
- National Institute for Health and Clinical Excellence. NICE TA450. Accessed 13 February 2019 via www.nice.org.uk
- Summary of Product Characteristics Blinatumomab (Amgen) accessed 13 February 2019 via www.medicines.org.uk

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