Atezolizumab & Bevacizumab (HCC)

Indication

Advanced or unresectable hepatocellular carcinoma (HCC) in patients who have not had previous systemic treatment with Child Pugh A liver impairment and WHO PS 0 or 1.

(TA666)

ICD-10 codes

C22

Regimen details

Day	Drug	Dose	Route
1	Atezolizumab	1200mg (flat dose)	IV infusion
1	Bevacizumab	15mg/kg	IV infusion

Cycle frequency

21 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Atezolizumab is administered in 250mL sodium chloride 0.9% over 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 minutes.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions discontinue treatment.

Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 to 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%. The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Bevacizumab should not be initiated for at least 28 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 28 days following surgery. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Pre-medication

Nil

Emetogenicity

This regimen has low emetic potential – refer to local policy

Additional supportive medication

Loperamide if required.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation

Atezolizumab and Bevacizumab are neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	14 days
Blood pressure (BP)*	on day 1
Proteinuria (dipstick)	on day 1

*Pre-existing hypertension should be adequately controlled before commencing treatment with bevacizumab.

Cardiac assessment is also required with ECHO for patients with significant cardiac history or prior chest wall radiation or anthracycline treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days
Blood pressure	Before each bevacizumab dose (more frequently if hypertension#)
Proteinuria (dipstick)	Before each bevacizumab dose

*every cycle for the first 12 weeks then every other cycle.
#Patients should be encouraged to monitor their blood pressure regularly at home

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9 /L
Platelets	≥ 75 x 10^9 /L
White cell count	>2.0 x 10^9 /L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 2.5 x ULN
Blood pressure	See bevacizumab toxicity section below
Proteinuria (dipstick)	See bevacizumab toxicity section below

Dose modifications

Dose modifications are not recommended for atezolizumab or bevacizumab. Treatment should be withheld or discontinued.

If either atezolizumab or bevacizumab has to be discontinued on account of toxicity and the patient is otherwise benefitting from therapy, treatment may continue with the remaining agent until disease progression or unacceptable toxicity.

- **Haematological toxicity**

Discuss with the consultant if:
WBC <2.0 x 10^9 /L
Neutrophils <1.0 x 10^9 /L
Platelets <75 x 10^9 /L

- **Renal impairment**

Atezolizumab - No modifications required for mild to moderate renal impairment. Atezolizumab has not been studied in severe renal impairment (GFR<30mL/min) but no need for dose adjustment is expected.

Bevacizumab – There is limited data on administering bevacizumab in renal impairment but no need for dose adjustment is expected. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Hepatic impairment**

Atezolizumab - No modifications required for mild hepatic impairment. Atezolizumab has not been studies in moderate or severe hepatic impairment (Child Pugh B & C) but no need for dose adjustment is expected.

Bevacizumab - There is no data of administering bevacizumab in patients with hepatic impairment but no need for dose adjustment is expected. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Other toxicities**

Atezolizumab:
For suspected immune related adverse events, atezolizumab should be withheld and corticosteroids administered. Once symptoms resolved to ≤Grade 1, the corticosteroids should be tapered over 1 month.

Toxicity	Definition	Dose adjustment
Pneumonitis	Grade 2	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent)
	Grade 3 - 4	Permanently discontinue
Hepatitis	Bilirubin 1.5 – 3 x ULN and/or AST/ALT 3-10 x ULN (if <ULN at baseline) *or* AST/ALT 5-10 x ULN (if 1-3 x ULN at baseline) *or* AST/ALT 8-10 x ULN (if 3-5 x ULN at baseline)	Withhold treatment if persists for more than 5-7 days. Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent)
	Bilirubin > 3 x ULN and/or AST/ALT > 10 x ULN	Permanently discontinue

Colitis	Grade 2 -3 diarrhoea or symptomatic colitis	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent)
	Grade 4 diarrhoea	Permanently discontinue
Hypothyroidism	Symptomatic or TSH >10	Withhold treatment Treatment may resume once symptoms controlled with thyroid replacement and TSH levels reducing If asymptomatic and TSH <10, continue treatment and repeat next cycle.
Hyperthyroidism	Symptomatic	Withhold treatment Treatment may resume once symptoms controlled with anti-thyroid medications and thyroid function improving If asymptomatic, continue treatment and repeat next cycle.
Adrenal insufficiency	Symptomatic	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent) and patient is stable on replacement therapy.
Hypophysitis	Grade 2 – 3	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent) and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue
Insulin dependent diabetes mellitus	Grade 3 – 4 hyperglycaemia	Withhold treatment Resume once metabolic control achieved with insulin therapy
Rash	Grade 3	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent)
	Grade 4	Permanently discontinue
Myasthenic syndrome/ myasthenia Gravis/ Guillain-Barre syndrome	Any grade	Permanently discontinue
Pancreatitis	Grade 2 – 3 (or Grade 3–4 increase in amylase or lipase)	Withhold treatment Resume once amylase and lipase levels ≤ Grade 1 (within 12 weeks) and when prednisolone reduced to ≤ 10mg/day (or equivalent) and patient is stable on replacement therapy
	Grade 4 or recurrent pancreatitis	Permanently discontinue

Permanently discontinue atezolizumab in patients with the following symptoms:

- Any grade 4 toxicity, except endocrinopathies that are controlled with replacement hormones.
- Any recurrent Grade 3 toxicity.
- Any treatment related toxicity that does not resolve to ≤ Grade 1 within 12 weeks after onset.
- If a corticosteroid dose ≥ 10mg/day prednisolone (or equivalent) is required for toxicity beyond 12 weeks after onset.

Bevacizumab:

Toxicity	Definition	Dose adjustment
Infusion related reactions	Grade ≤ 2	**90 minute infusion:** premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion:** all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion:** all subsequent doses should be given over 60 minutes with premedication.
	Grade > 2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal If 140/90 mmHg – 150/100mmHg – administer and recheck BP 48 hours later. Commence antihypertensive if BP remains > 140/90mmHg. - if >150/100 mmHg – omit and recheck BP 48 hours later (commence antihypertensive if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 Persistent BP > 140/90 mmHg, requiring increase in antihypertensive treatment	Withhold bevacizumab. If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.
	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour analysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab.

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

- **Serious side effects**

Immune reactions
Interstitial lung disease, pneumonitis
Pancreatitis
Hepatitis
Colitis
Neuropathies
Endocrinopathies
Infusion related toxicity
Arterial/venous thromboembolism
GI perforation, fistulas
Haemorrhage
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Congestive heart failure
Wound healing complications

- **Frequently occurring side effects**

Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypertension, hypotension
Dyspnoea
Nausea, vomiting
Diarrhoea
Rash
Pruritis
Arthralgia
Fatigue
Proteinuria
Abdominal pain
Infections

- **Other side effects**

Decreased appetite
Altered electrolytes
Raised transaminases
Guillain-Barre syndrome

Significant drug interactions – for full details consult product literature/ reference texts
No documented significant pharmacokinetic interactions have been reported with bevacizumab or atezolizumab.

Corticosteroids: the use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.

Additional comments

Bevacizumab is contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies.
Bevacizumab should be used with caution in patients with:

- Untreated central nervous system metastases
- Uncontrolled hypertension
- History or risk factors for thromboembolic events
- Significant cardiac risk factors for development of congestive heart failure

Patients should be issued with an Atezolizumab Patient Alert Card and advised to carry the card with them at all times.

References

- Finn RS, Cheng AL. Atezolizumab and Bevacizumab in Hepatocellular Carcinoma. N Engl J Med. 2020 382(20):1894-1905
- National Institute for Health and Care Excellence TA666 accessed 7 February 2023 via www.nice.org.uk
- Summary of Product Characteristics Atezolizumab - Tecentriq® (Roche) accessed 7 February 2023 via www.medicines.org.uk
- Summary of Product Characteristics Bevacizumab - Avastin® (Roche) accessed 7 February 2023 via www.medicines.org.uk

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