Chemotherapy Protocol

GENITOURINARY CANCER

Atezolizumab

Regimen

- Bladder – Atezolizumab

Indication

- The treatment of adult patients with locally advanced or metastatic urothelial carcinoma after disease progression following one prior platinum containing regimen regardless of the setting (neoadjuvant, adjuvant, metastatic)

- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Atezolizumab	Fatigue, rash, pruritis, pneumonitis, colitis, pacreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, LFTs and U&Es prior to day one of each cycle

- Thyroid function tests prior to starting treatment and then every 6 weeks or when clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle no dose reductions are recommended for atezolizumab. The preference is to delay the dose or discontinue treatment.

Please discuss all treatment delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

There are no standard dose adjustments for haematological toxicity with atezolizumab treatment.

Hepatic Impairment

For patients with pre-existing mild hepatic impairment no dose adjustment is recommended. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment.

For a NCI-CTC grade 2 hepatitis (ALT or AST between 3-5xULN or a bilirubin between 1.5-3xULN) that persists for between 5-7 days then withhold the atezolizumab and consider treatment with a corticosteroid. The corticosteroid may be tapered over at least one month if the LFTs improve. Treatment with atezolizumab may be resumed when the event improves to grade 1 or below within 12 weeks and the corticosteroid dose has been reduced to the equivalent of oral prednisolone 10mg per day or less.

For a grade 3 or above hepatitis (ALT or AST greater than 5xULN or bilirubin greater than 3xULN) permanently discontinue atezolizumab.

Renal Impairment

No dose adjustment is required in patients with pre-existing renal impairment.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Atezolizumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity, likely to be related to its pharmacology.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset month’s after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and atezolizumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Atezolizumab should be permanently discontinued for: any NCI-CTC grade 3 or 4 pneumonitis or hepatitis; any other life threatening NCI-CTC grade 4 reaction (including colitis and renal impairment); any recurrence of a severe or NCI-CTC grade 3 reaction; any persistent NCI-CTC grade 2 or 3 treatment-related adverse

reaction that does not recover to grade 1 or resolve within 12 weeks after the last dose.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold until symptoms resolve and radiographic abnormalities improve. Consider treatment with oral prednisolone 1-2mg/kg or equivalent per day Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day.
	Grade 3 or 4 pneumonitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune- related colitis	Grade 2 or 3 diarrhoea or symptomatic colitis	Withhold the atezolizumab initially. For a grade 2 diarrhoea or colitis, if the symptoms persist for more than 5 days or recur, start treatment with 1-2mg/kg oral prednisolone or equivalent per day For a grade 3 diarrhoea or colitis treatment with intravenous corticosteroids should be started, this may be converted to oral treatment as symptoms improve. If the symptoms improve to grade 1 or less taper the corticosteroids over one month Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day
	Grade 4 diarrhoea or colitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune-related pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (more than 2xULN) or grade 2 or 3 pancreatitis	Withhold atezolizumab Treatment with atezolizumab may be resumed if serum amylase and lipase levels improve to grade 0 or

		grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to 10mg or less oral prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune-related thyroid disorders	Symptomatic	Withhold atezolizumab *Hypothyroidism* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism* Treatment may be resumed when symptoms are controlled by cabimazole or equivalent and thyroid function is improving
Immune-related adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed if the symptoms improve to grade 0 or grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10mg or less of oral prednisone or equivalent per day and patient is stable on replacement therapy
Immune-related diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose more than 250-500mg/dL)	Withhold atezolizumab Treatment may be resumed if metabolic control is achieved on insulin replacement therapy
Immune-related myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome and meningoencephalitis	All grades	Permanently discontinue atezolizumab
Infusion related reactions	Grade 1	Reduce the infusion rate to half

		Once the event has resolved, wait for 30minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to original rate
	Grade 2	Withhold atezolizumab Restart at half of the infusion rate only after the symptoms have resolved
	Grade 4	Permanently discontinue atezolizumab
Immune-related rash	Grade 3 rash	Withhold atezolizumab Treatment may be resumed if the rash is resolved and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day
	Grade 4 rash	Permanently discontinue atezolizumab. Consider treatment with corticosteroids

Regimen

21 day cycle until loss of clinical benefit or unmanageable toxicity (12 cycles will be set in Aria)

Drug	Dose	Days	Route
Atezolizumab	1200mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Dose Information

- If a planned dose of atezolizumab is missed, it should be administered as soon as possible. Do not wait until the next planned dose. The schedule of administration must be adjusted to maintain a 21 day period between doses.

Administration Information

Extravasation

- Atezolizumab – neutral

Other

- The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over

30minutes.

- Please refer to the toxicity table above for the actions to be taken in relation to infusion related reactions.

Additional Therapy

- No antiemetics are required
- As required for the treatment of infusion related reactions;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- Loperamide 4mg oral initially followed by 2mg after each loose stool when required for the relief of diarrhoea (maximum 16mg/24 hours).
- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- The use of systemic corticosteroids, before starting treatment with atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting atezolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of atezolizumab.
- Patients must be given an atezolizumab Patient Alert Card.

Coding

- Procurement – X
- Delivery – X

References

1. Balar AV, Galsky MD, Rosenberg JE et al. Atezolizumab as a first line treatment in cisplatin ineligible patients with locally advanced and metastatic urothelial carcinoma; a single arm multicentre phase two trial. Lancer 2017; 389 (10064): 67-76.

REGIMEN SUMMARY

Atezolizumab

Day One

1. Atezolizumab 1200mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30minutes.

   Ensure the patient has been an atezolizumab patient alert card.

2. Chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions

3. Hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions

4. Paracetamol 1000mg oral when required for the relief of infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	April 2017	None	Dr Deborah Wright Pharmacist	Dr Simon Crabb Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.