Chemotherapy Protocol

BLADDER CANCER

Pembrolizumab (400mg)

Regimen

- Bladder – Pembrolizumab (400mg)

Indication

- Pembrolizumab is indicated for locally advanced (ie T4b any N or any T N2-3 disease) or metastatic (any T any N M1 disease) transitional cell carcinoma of the urothelial tract cancer previously treated with platinum-based chemotherapy where;

  - There has been disease progression during or following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic urothelial cancer

  - The patient has either: not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed less than or equal to 12 months since completing the platinum-based chemotherapy

  Pembrolizumab is also indicated as first line treatment of locally advanced or metastatic urothelial cancer in patients who are ineligible for cisplatin-based chemotherapy where;

  - the patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy for localised urothelial cancer OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy for localised urothelial cancer, has relapsed more than 12 months since completing the platinum-based chemotherapy

  - The patient is ineligible for platinum-based chemotherapy, due to one or more of the following:
    (a) impaired renal function (EDTA-assessed glomerular filtration rate greater than 30 and less than 60mls/min),
    (b) hearing loss of 25dB or more as assessed by formal audiometry,
    (c) NCI CTCAE grade 2 or worse peripheral neuropathy

  In both indications the following criteria also apply;

  - The patient has no symptomatically active brain metastases or leptomeningeal metastases

  - The patient has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PDL2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody unless it was received as part of the

pembrolizumab compassionate use programme for this indication and the patient meets all other criteria listed here

- Pembrolizumab must be given as monotherapy
- A formal medical review as to whether treatment with pembrolizumab should continue or not will be scheduled to occur at least by the end of the third cycle of treatment
- The patient is to be treated until disease progression and loss of clinical benefit or excessive toxicity or patient choice, whichever is the sooner. The maximum duration of treatment is two years
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Pembrolizumab	Pneumonitis, nephritis, colitis, thyroid disorders, hypophysitis, infusion related reactions, hepatitis

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 before each administration (cycle) or when clinically indicated.

Dose Modifications

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

Pembrolizumab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site specific specialist teams or oncologists / haematologists with experience of prescribing these agents. Clinicians should be aware that the current funding approval for pembrolizumab precludes further treatment after an interruption of 12 weeks or longer; this situation may change.

Please discuss all dose reductions / 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 is little need to adjust the dose of pembrolizumab for haematological toxicity.

Hepatic Impairment

For a hepatitis associated with an AST / ALT of 3-5xULN and / or a total bilirubin of 1.5-3xULN then withhold treatment and administer corticosteroids. Upon improvement to NCI-CTC grade 1 hepatic injury begin to taper the corticosteroid over a period of one month. The pembrolizumab may be re-started when the liver function remains at NCI-CTC grade 1 following corticosteroid taper.

The pembrolizumab should be permanently discontinued when the hepatic injury does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Pembrolizumab should be permanently discontinued in the first instance when hepatitis develops that is associated with an AST / ALT equal to or greater than 5xULN, an increase in AST / ALT of 50% or greater relative to baseline and that lasts at least one week in patients with liver metastasis who begin treatment with moderate (grade 2) elevation of AST / ALT or where the bilirubin is greater than 3xULN.

Renal Impairment

Where a NCI-CTC grade 2 nephritis develops withhold treatment and administer corticosteroids. Upon improvement to NCI-CTC grade 1 or less, initiate corticosteroid taper over at least one month. Pembrolizumab may be resumed when the reaction remains at NCI-CTC grade 1 or below following tapering of the corticosteroid.

The pembrolizumab should be permanently discontinued when the nephritis does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Pembrolizumab should be permanently discontinued for any NCI-CTC grade 3 or above nephritis.

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.

Pembrolizumab 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 months 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 pembrolizumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Pembrolizumab should be permanently discontinued for any NCI-CTC grade 3 or 4 pneumonitis, nephritis, infusion related reaction or a NCI-CTC grade 4 adverse reaction.

Endocrine

Pembrolizumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism. This may present with nonspecific symptoms resembling other causes such as brain metastasis or underlying disease.

Isolated hypothyroidism can be managed with replacement therapy, without treatment interruption or corticosteroids.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of intravenous corticosteroids with mineralocorticoid activity is recommended, the patient must be evaluated for presence of sepsis or infections. If there are signs of adrenal insufficiency but the patient is not in crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy is recommended to treat the gland inflammation. The scheduled dose of pembrolizumab should be omitted. It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with pembrolizumab may be resumed and initiation of corticosteroid taper should be based on clinical judgment.

Hypophysitis can present as a diffuse, heterogenous enlargement of the pituitary on a brain MRI but can be completely normal. When hypophysitis with pituitary dysfunction is suspected, blood tests including thyroid stimulating hormone (TSH), free T4, adrenocorticotropic stimulating hormone, cortisol, leutinizing hormone, and follicle-stimulating hormone should be obtained in women, and the first four plus testosterone in men. Typically the anterior pituitary axis is involved, affecting thyroid, gonadal, and adrenal function, but isolated axis dysfunction can be seen. Hypophysitis will cause low free T4 as well as TSH. Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities such as hyponatremia and hyperkalemia constitutes adrenal crisis. Hospitalization and intravenous steroids with mineralocorticoid activity, such as methylprednisolone, should be initiated while waiting for laboratory results. Infection

and sepsis should be ruled out with appropriate cultures and imaging. Prednisolone 1 mg/kg by mouth should be administered if patients are clinically stable. Steroids can usually be tapered over 30 days to achieve physiologic replacement levels. Thyroid hormone and/or testosterone replacement therapy may not be permanent, as the need for those hormones may wane over months in some patients. Cortisone replacement may also not be permanent in a modest portion of patients.

Eye

Uveitis is associated with pembrolizumab. All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). For NCI-CTC grade 1-2 events evaluation by an ophthalmologist is recommended. Treatment with topical corticosteroids eye drops and iridocyclitics can be tried. Discontinue pembrolizumab if symptoms persist despite treatment with topical immunosuppressive therapy. Discontinue pembrolizumab for NCI-CTC grade 3 or above ocular symptoms and consider treatment with systemic corticosteroids. When symptoms improve to NCI-CTC grade 1 then taper the corticosteroids over at least four weeks.

Gastrointestinal

Gastro-intestinal immune reactions include diarrhoea, increased frequency of bowel movements, abdominal pain or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of pembrolizumab must be promptly evaluated to exclude infectious or other alternate causes. Immune-related colitis is often associated with evidence of mucosal inflammation, with or without ulcerations and lymphocytic and neutrophilic infiltration.

NCI-CTC grade 1 diarrhoea or suspected mild colitis may continue on pembrolizumab. Symptomatic treatment and close monitoring are advised.

For NCI-CTC grade 2 – 3 colitis withhold the pembrolizumab and administer corticosteroids. Upon improvement to NCI-CTC grade 1 colitis begin to taper the corticosteroid over a period of one month. The pembrolizumab may be re-started when the colitis remains at NCI-CTC grade 1 following corticosteroid taper.

The pembrolizumab should be permanently discontinued when the colitis does not improve to at least NCI-CTC grade 1 within 12 weeks of the last dose, the corticosteroid dose cannot be reduced to 10mg or less of prednisolone or equivalent per day within 12 weeks or any NCI-CTC grade 3 or above reaction.

Lung

Interstitial lung disease including pneumonitis and acute interstitial pneumonitis are associated with pembrolizumab. For NCI-CTC grade 1 events (asymptomatic with radiographic findings only) then the pembrolizumab may be continued with close monitoring. Radiologic findings should be followed on serial imaging studies and consideration given to pulmonary consultation and/or bronchoscopy, if clinically indicated. For NCI-CTC grade 2 events withhold the pembrolizumab and consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL) and pulmonary function tests. Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to NCI-CTC grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Treatment with pembrolizumab may be resumed if the event improves to NCI-CTC

grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of prednisolone 10 mg oral daily or less. Repeat chest imaging monthly as clinically indicated.

Should a second episode of pneumonitis occur then discontinue pembrolizumab.

For NCI-CTC grade 3 or 4 events discontinue pembrolizumab and consider pulmonary function tests and seek advice from a lung specialist. A bronchoscopy with biopsy and / Or BAL should be considered. Treatment involves corticosteroid therapy such as intravenous methylprednisolone 125mg. When symptoms improve to NCI-CTC grade 1 or less, a high dose oral steroid such as prednisone 1 to 2 mg/kg once per day can be considered. A reducing schedule should be considered over a period of at least four weeks.taper should be started and continued over no less than 4 weeks. If intravenous corticosteroids followed by high dose oral corticosteroids do not reduce initial symptoms within 48 to 72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose followed by a more prolonged taper and administer infliximab.

Skin

Serious skin reactions include dermatitis exfoliative, erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis. Pembrolizumab can also be associated with pruritus, rash, (generalized and maculo-papular) and vitiligo. All attempts should be made to rule out other causes such as metastatic disease, infection or allergic dermatitis.

For NCI-CTC grade 1-2 skin reactions try symptomatic treatments such as topical corticosteroids or urea-containing creams in combination with oral antipruritics. Pembrolizumab can continue.

For NCI-CTC grade 3 or above events withhold the pembrolizumab and consider a dermatology referral. Treatment with systemic corticosteroids such as prednisolone 1mg/kg each day may be necessary. When symptoms improve to NCI-CTC grade 1 or less then steroid taper should be started and continued over no less than 4 weeks.

Regimen

42 day cycle for 18 cycles (two years)

Drug	Dose	Days	Route
Pembrolizumab	400mg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes with a 0.2 micron filter

Administration Information

Extravasation

- Pembrolizumab – neutral

Other

- Pembrolizumab should be administered using a low protein binding filter.

Additional Therapy

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

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

- 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 pembrolizumab 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 pembrolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of pembrolizumab.

Coding

- Procurement – X71.5
- Delivery – X72.3

References

1. National Institute for Health and Care Excellence (2018) Technology Appraisal 519. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum containing chemotherapy. DOH:London.

REGIMEN SUMMARY

Pembrolizumab (400mg)

Day One

1. Pembrolizumab 400mg intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
   Administration Instructions
   Pembrolizumab should be administered using a low protein binding filter

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
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2019	None	Dr Deborah Wright Pharmacist	Dr Mathew Wheater 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 which occur as a result of following these guidelines.