

Chemotherapy Protocol

SKIN CANCER

IPILIMUMAB

Regimen

- Skin – Ipilimumab

Indication

- Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
- Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
- WHO performance status 0, 1

Toxicity

| Drug | Adverse Effect |
|------------|----------------------------------------------------------------------------------------------------------------------|
| Ipilimumab | Colitis, diarrhoea, dermatitis, neuropathy, hypothyroidism, hepatotoxicity, infusion related reactions, hypophysitis |

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

Monitoring

Regimen

- FBC, LFT's and U&E's prior to day one of each cycle
- Blood pressure prior to treatment
- 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.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

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

There is little need to adjust the dose of ipilimumab for haematological toxicity.

Hepatic Impairment

Immune related hepatic reactions are associated with ipilimumab.

For patients with elevated AST or ALT in the range of 5-8xULN or total bilirubin in the range of 3-5xULN that is suspected to be related to ipilimumab, the scheduled dose of ipilimumab should be withheld until the LFTs have resolved to these levels. Treatment may then be restarted.

For patients with AST or ALT elevations greater than 8xULN or bilirubin greater than 5xULN that are suspected to be related to ipilimumab, then the ipilimumab must be permanently discontinued and appropriate supportive treatment initiated.

Renal Impairment

No dose reductions are necessary in mild to moderate 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.

Ipilimumab 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 ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Endocrine

Ipilimumab 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.

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 ipilimumab 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 ipilimumab 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, adrenocorticotrophic 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.

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 ipilimumab 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 or 2 diarrhoea or suspected mild to moderate colitis may continue on ipilimumab. Symptomatic treatment and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of ipilimumab should be omitted and consideration given to prescribing prednisolone 1 mg/kg orally once a day. If resolution to NCI-CTC grades 0-1 or return to baseline occurs, the ipilimumab may be resumed at the next scheduled dose.

Doses omitted due to an adverse reaction must not be replaced. Consider endoscopy to confirm or rule out colitis if there is persistent NCI-CTC grade 2 diarrhoea or NCI-CTC grade 1 - 2 diarrhoea with bleeding.

Ipilimumab must be discontinued if NCI-CTC grade 3 or 4 diarrhoea, colitis, peritoneal signs of bowel perforation, ileus or fever occur. High-dose intravenous corticosteroid therapy should be initiated immediately unless bowel perforation is present. Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment (tapering over 6-8 weeks). In clinical trials, rapid tapering (over periods of less than 1 month) resulted in recurrence of diarrhoea or colitis in some patients. Consider alternative immunosuppressive therapy (eg single dose of infliximab 5mg/kg) if symptoms do not respond to steroids in 5-7 days.

Neurological

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days must be evaluated and other causes excluded.

For patients with NCI-CTC grade 2, neuropathy likely related to be related to ipilimumab omit the scheduled dose. If the neurologic symptoms resolve to baseline, the patient may resume treatment at the next scheduled dose.

Ipilimumab must be permanently discontinued in patients with NCI-CTC grade 3 or 4, sensory neuropathy. Patients must be treated according to local guidelines for management of sensory neuropathy.

Skin

A diffuse, erythematous maculopapular rash that can be intensely pruritic was observed in 47% to 68% of patients, starting an average of 3 to 4 weeks after ipilimumab.

NCI-CTC grade 1 or 2 skin reactions may remain on ipilimumab therapy with symptomatic treatment such as topical corticosteroids and antihistamines. For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids consider oral corticosteroid therapy (e.g. prednisolone 1 mg/kg once a day).

For patients with NCI-CTC grade 3 symptomatic skin reactions, the scheduled dose of ipilimumab should be omitted. If initial symptoms improve to NCI-CTC grade 1 or resolve then the ipilimumab therapy may be resumed at the next scheduled dose. Ipilimumab must be permanently discontinued in patients with a NCI-CTC grade 4 rash or grade 3 pruritus and consideration given to systemic corticosteroid therapy.

Other Immune-Related Adverse Reactions

The following additional adverse reactions, suspected to be immune-related, have been reported and include uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, haemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported. If these occur at NCI-CTC grade 3 or above then consider immediate high-dose corticosteroid therapy and discontinuation of ipilimumab.

For ipilimumab-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

[Regimen](#)

21 day cycle for 4 cycles

| Drug | Dose | Days | Route |
|------------|--------|------|--------------------------------------------------------------------|
| Ipilimumab | 3mg/kg | 1 | Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes |

[Dose Information](#)

- Ipilimumab will be dose banded as per the CSCCN agreed bands

[Administration Information](#)

Extravasation

- Ipilimumab – neutral

Other

- Ipilimumab should be administered using a low protein binding filter
- The final concentration of ipilimumab should be between 1-4mg/ml

[Additional Therapy](#)

- No antiemetics are required
- When required for infusion related reactions
 - chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions
 - hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions
 - paracetamol 1000mg oral when required for the relief of infusion related reactions
- Gastric protection with a proton pump inhibitor or a H₂ 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 ipilimumab should be avoided ipilimumab because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids can be used after starting ipilimumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of ipilimumab.

Coding

- Procurement – X71.5
- Delivery – X72.2

References

1. NICE Technology Appraisal 319. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. July 2014. DOH: London
2. NICE Technology Appraisal 268. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. Dec 2012. DOH: London

REGIMEN SUMMARY

Ipilimumab

Day One

1. Ipilimumab 3mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes
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 |
|---------|---------------|-------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------|
| 1.1 | April 2015 | Treatment for infusion related reactions changed to "as required" | Dr Deborah Wright Pharmacist | Prof C Ottensmeier Consultant Medical Oncologist Dr M Wheeler Consultant Medical Oncologist |
| 1 | February 2015 | None | Dr Deborah Wright Pharmacist | Prof C Ottensmeier Consultant Medical Oncologist Dr M Wheeler 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.