Systemic Anti-Cancer Treatment Protocol

Abiraterone

PROCTOCOL REF: MPHAABIRA
(Version No: 1.2)

This protocol has been temporarily amended-please see the ORAL SACT OPERATIONAL CHANGES DURING COVID -19

Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Approved for use in:

- The treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- The treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen

****BlueTeq registration required ****

Dosage:

Drug	Dosage	Route	Frequency
Abiraterone	1000mg	Oral	Daily
Prednisolone	10mg	Oral	Daily

Continuous until disease progression or unacceptable toxicity

Prednisolone can be switched to dexamethasone 500 micrograms daily.

Supportive treatments:

No routine supportive treatments recommended

Extravasation risk:

Not applicable

Administration:

The tablets must be swallowed whole with water as a single daily dose and **must not** be taken with food.

Counselling points
The recommended dose is 1,000 mg (two 500mg tablets) as a single daily dose that **must not** be taken with food, i.e. no food for two hours before and one hour after. Taking the tablets with food increases systemic exposure to abiraterone and therefore increases possibility of adverse effects Abiraterone must be taken with low dose steroids. Contraception in males It is not known whether abiraterone or its metabolites are present in semen. Appropriate contraception must be used if the patients partner is of child bearing potential.

Drug Interactions

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Spironolactone may increase prostate specific antigen (PSA) levels. Use with abiraterone is **not** recommended.

Main Toxicities:

Adverse reactions	
System Organ Class	**Adverse reaction and frequency**
Infections and infestations	very common: urinary tract infection common: sepsis
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased [b] rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash

Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased
** Fractures includes osteoporosis and all fractures with the exception of pathological fractures
[a] Spontaneous reports from post-marketing experience
[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

Investigations and Treatment Plan:

Cycle	Pre	C1	C1	C2	C2	C3	Ongoing
Week		**1**	**3**	**5**	**7**	**9**	
Clinical Assessment	X	X		X		X	Every cycle
SACT assessment			X	X	X	X	Every review
FBC	X		X	X	X	X	Every 2 weeks for the first three cycles and monthly thereafter
U&E & LFTs	X		X	X	X	X	Every 2 weeks for the first three cycles and monthly thereafter
PSA	X	X		X		X	Every 4 weeks
CT scan	X						Every 24 weeks as clinically indicated
Informed Consent	X						First cycle only
Blood pressure measurement	X	X	X	X	X	X	Every Review
PS recorded	X	X	X	X	X	X	Every Review
Toxicities documented	X	X	X	X	X	X	Every review
Weight recorded	X	X		X		X	Every cycle

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Abiraterone is not myelosuppressive but FBC should be reviewed prior to each cycle.

If neutrophils < 1.0 x 10^9/L and/or platelets < 100x 10^9/L, continue drug therapy but **discuss with the clinical team prior to the next cycle.** If neutrophils < 0.5 x 10^9/L and/or platelets < 50x 10^9/L, **discuss with the clinical team before continuing treatment**

Non-haematological toxicity:

Blood Pressure Guidance:

- Pre-existing hypertension should be controlled (usually via the GP) before treatment with abiraterone starts.
- Baseline blood pressure should be < 150/100mmHg.

Blood pressure measurements	
Systolic 140-150 mmHg or Diastolic <90 mmHg:	Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary
Systolic 150-160mmHg or Diastolic 90-100mmgh:	-Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg.
Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):	Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg
Severe hypertension (>180mmHg systolic or >110mmHg diastolic)	Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled.

NICE Clinical Guideline CG 127- Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/CG127Hypertension in adults: diagnosis and management | Guidance and guidelines | NICE

- For previously untreated patients > 55 years, use a calcium channel blocker first-line.

- Monitoring of BP and management until stabilised, may require GP involvement.

Hypokalaemia:

- Pre-existing hypokalaemia should be corrected before abiraterone treatment starts.
- Consider maintaining potassium level at ≥4.0mM

Hypokalaemia	
Potassium: 3.0 – 3.5 mmol/L (Mild)	Continue abiraterone, manage hypokalaemia according to local guidelines (aim for oral replacement)
Potassium: < 3.0 mmol/L (moderate-severe)	Withhold abiraterone until K+ has recovered to normal limits and manage hypokalaemia according to local guidelines

Treatment of Hypokalaemia in Adults Guideline is available on the staff extranet via the link below:
https://extranet.clatterbridgecc.nhs.uk/index.php/intranet/policies-and-corporate-documents/guidelines/clinical

Renal impairment
Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction. However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Hepatic impairment	
Grade 1 AST or ALT increase to 2.5 times the upper limit of normal (ULN) Bilirubin increase to 1.5 times ULN	Repeat LFTs at two-weekly intervals. No dose reduction is required.
Grade 2 AST or ALT increase to 2.5 to 5 times ULN Bilirubin increase to 1.5 to 3 times ULN	Repeat LFTs one a week No dose reduction is required
Grade 3 AST or ALT over 5 times the ULN Bilirubin over 3 times the ULN	Withhold treatment immediately, along with any other potentially hepatotoxic medications. Repeat LFTs weekly until return to baseline or grade 1. Re-treatment following return of liver function tests to the patient's baseline at reduced dose of 500mg (one tablet) once daily. Patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose treatment should be discontinued.
Grade 4 AST or ALT 20 times the ULN Bilirubin to 10 times the ULN	Treatment should be discontinued and patients should not be re-treated.

Abiraterone may be use with caution in patients with pre-existing moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. No dose adjustment is currently recommended for this group of patients. Abiraterone should not be used in patients with pre-existing severe hepatic impairment.

References:

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NICE Technology Appraisal 259

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