Abiraterone (high-risk, hormone sensitive, non-metastatic prostate cancer)

Indication
High-risk, hormone sensitive, non-metastatic prostate cancer

Regimen details
Abiraterone 1000mg orally daily
Prednisolone 5mg orally daily then weaned slowly after 2 years (see below)*

(Patient should have been started on androgen deprivation therapy no more than 3 months prior to starting abiraterone)

Cycle frequency
Continuous treatment, dispense every 3 months for 2 years

Number of cycles
9 cycles (dispensed at 3-monthly intervals)
9th cycle will consist of 2 months of treatment followed by a reducing course of prednisolone*

Administration
Available as 500mg tablets

Abiraterone should be taken at least 2 hours after food and no food should be eaten for at least 1 hour after. Taking food with abiraterone can increase absorption by up to 10 times and therefore can increase toxicity
Steroids should be tapered off slowly when treatment is withdrawn

Prednisolone should be taken each morning with food.

*** Prednisolone weaning** -
When patients have been on prednisolone for long durations this should not be stopped abruptly as this may lead to adrenal insufficiency. After the 2 years of treatment once Abiraterone has stopped we advise;
- reduce prednisolone dose by 1mg every 4 weeks over a 16-week period.

A prednisolone reducing course will be prescribed automatically with the final cycle of treatment, however, patients stopping treatment prematurely should be weaned off prednisolone as described above

Pre-medication
n/a

Emetogenicity
n/a

Additional supportive medication
PPI should be prescribed concurrently
Patients should continue on androgen deprivation therapy

Extravasation
n/a

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Testosterone	14 days
PSA	14 days
Blood pressure	baseline

Investigations –pre subsequent cycles

FBC, U&Es, LFTs, PSA

BP and LFTs should be checked every 2 weeks for the first 3 months then every 4 weeks thereafter. Patients will be encouraged to purchase ambulatory BP monitors or alternatively arrange for BP checks with GP.

Cautions:

Severe renal impairment
Hepatic impairment (do not use if severe)
Uncontrolled hypertension
History of pituitary or adrenal dysfunction
Contraindication to steroids e.g. poorly controlled diabetes mellitus, active peptic ulceration
Concomitant treatment with strong inducers of CYP3A4

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by chemotherapy staff nurses or prescriber/ consultant.

See under "Dose modifications" below

Dose modifications

For liver toxicity, see table below
For other grade 3 toxicities, suspend treatment. Restart when resolved.

Liver Toxicities

TOXICITY EVENT	ACTION
Grade 1 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN)	The frequency of liver function test monitoring should be increased. No dose reduction is required
Grade 2 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN)	The frequency of liver function test monitoring should be increased to ≥ once a week. No dose reduction is required
Grade 3 or 4 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >5X ULN; increase in total bilirubin to >3X ULN),	Hold abiraterone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1. **Please inform clinician**
Grade 4 increases in AST, ALT or bilirubin (e.g. increase in AST or ALT to >20x ULN; increase in total bilirubin to >10x ULN)	Discontinue abiraterone immediately. Do not rechallenge. Follow-up until resolution of

	abnormal liver function tests. **Abiraterone should not be re-introduced. Please inform clinician**
RE-CHALLENGE AFTER GRADE 3 ***Please discuss with clinician before re-challenge***	**ACTION**
If abiraterone resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin	Resume abiraterone with the first dose level reduction (3 tablets, 750mg) when Grade 3 toxicities resolve to Grade 1 or baseline.
If Grade 3 or higher increases in AST, ALT or bilirubin recur after the first dose reduction	Hold abiraterone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the liver function tests return to baseline value or Grade 1
If abiraterone resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction	Resume abiraterone with the second dose level reduction (2 tablets, 500mg) when AST, ALT or bilirubin returns to baseline value or Grade 1

Management of abiraterone associated hypokalaemia

TOXICITY EVENT	**ACTION**
Grade 1 (3.0 – 3.5mmol/L)	Continue abiraterone. Supplement with oral sando-K two tablets twice a day Exclude and manage other causes of hypokalemia Discuss with clinician about increasing prednisolone dose to 5mg BD. Monitor serum potassium twice weekly until stable or >4.5mmol/L
Grade 2 (3.0–3.5mmol/L and symptomatic)	Withhold abiraterone. Supplement with oral potassium K two tablets twice a day and monitor closely Exclude and manage other causes of hypokalaemia. Re-start abiraterone with close monitoring, discontinue if recurs. Monitor serum potassium twice weekly until stable or >4.5mmol/L Discuss with clinician about increasing prednisolone dose to 5mg BD.
Grade 3 (<3.0-2.5mmol/L) Or Grade 4 (<2.5mmol/L and life-threatening)	Discontinuation of abiraterone Arrange urgent hospitalisation for intravenous potassium replacement and cardiac monitoring. Inform clinician before re-starting abiraterone

Blood pressure parameters

TOXICITY EVENT	**ACTION**
BP repeatedly in range of 120-139/80-89 mmHg	Continue abiraterone
BP repeatedly in range of 140-159/90-99 mmHg	Continue abiraterone. Advise patient to arrange appointment with GP to start / increase anti-hypertensive medication within 7 days Recommend monitoring BP twice a day for following week
BP repeatedly ≥ 160/100 mmHg or life-threatening	Withhold abiraterone.

consequences of hypertension)	Advise urgent appointment with GP within 3 days to start / increase anti-hypertensive medication. Advise patient of red flag symptoms of severe hypertension (eg. Headaches, chest pains) which requires urgent medical assessment Recommend monitoring BP twice a day for following week
Re-challege; Once blood pressure resolves to being predominantly <140/90 or baseline	Resume at full dose of Abiraterone but increase **prednisolone to 5mg BD**. Please liaise with clinician.

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Cardiac failure
Arrhythmias
Hepatotoxicity
Adrenal insufficiency
Myopathy
Allergic alveolitis

- **Frequently occurring side effects**

Peripheral oedema
Fluid retention
Hypokalaemia
Hypertension
Urinary tract infection
Diarrhoea
Hyperglycaemia

- **Other side effects**

Fractures
Rash

Significant drug interactions

– for full details consult product literature/ reference texts

Medicinal products activated by or metabolised by CYP2D6 (e.g. metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol): caution is advised when abiraterone acetate is administered with medicinal products activated or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered.

Codeine, oxycodone and tramadol are metabolised via CYP2D6 to their active metabolites and so abiraterone may have an (as yet unknown) effect on patient's analgesic requirements if treated with these agents.

Strong inhibitors and inducers of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital): avoid or use with caution.

Spironolactone: binds to the androgen receptors and may increase PSA levels. Concomitant use not recommended.

References

Zytiga SPC - https://www.medicines.org.uk/emc/product/2381
Glucocorticoid (steroid) withdrawal SOP EBG00858. Dr Howell, Lancashire Teaching Hospitals Foundation Trust

THIS PROTOCOL HAS BEEN DIRECTED BY DR PORTNER, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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