The Clatterbridge
Cancer Centre
NHS Foundation Trust

Adrenal/Pituitary insufficiency following cancer immunotherapy

Chemotherapy, Immunotherapy, and Supportive Medicines

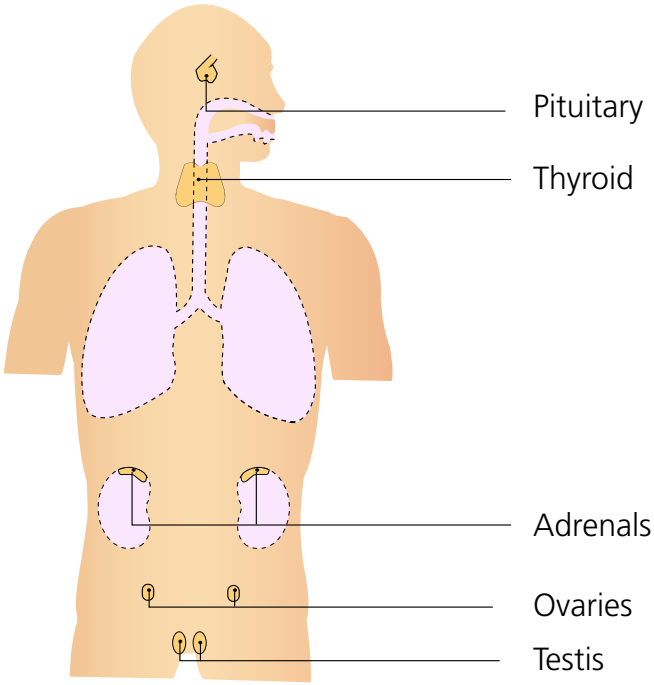
A guide for patients and carers

Contents

What are the adrenal glands?

Your doctor at The Clatterbridge Cancer Centre has prescribed a course of chemotherapy for you. This booklet tells you about chemotherapy and the chemotherapy service at The Clatterbridge Cancer Centre. We will also give you a leaflet about the treatment you will receive.

We hope this booklet and the leaflet will answer most of your questions and help you discuss your treatment with the doctors and nurses. Our medical and nursing staff are here to answer any questions you or your family may have.



What is the pituitary gland?

The pituitary gland is a gland in the brain that releases a number of hormones, which regulates the function of the adrenal glands, the thyroid gland and the testis or ovaries.

What is adrenal insufficiency?

Adrenal insufficiency occurs when your body is no longer able to produce sufficient amounts of cortisol and/or aldosterone. This may be for a number of reasons. In 90% of cases the reason is related to the over activity of the immune system. In some cases, this can happen spontaneously and is known as Addison's disease. In other cases, it can be a side effect of immunotherapy drugs. The immunotherapy, which is being used to treat your cancer, has activated the body's immune system. Sometimes the immune cells that have been activated go off target and act on your body's normal cells – in this case your adrenal glands. Another gland that can be affected is the pituitary gland (see the section below). Because the pituitary gland instructs the adrenal glands to work, if the immunotherapy has stopped the pituitary gland from working, then the adrenal glands also stop working (known as 'secondary insufficiency').

The symptoms of adrenal insufficiency are non-specific, and are often similar to symptoms of depression or flu:

A	appetite loss, unintentional weight loss
D	discolouration of skin
D	dehydration
I	increased thirst and need to urinate frequently
S	salt, soy sauce or liquorice cravings
O	oligomenorrhoea (irregular or infrequent periods in women)
N	no energy or motivation (fatigue, lethargy), low mood
S	sore/painful, weak muscles and joints

What is pituitary insufficiency?

This gland can become inflamed as a result of the immune system having off-target effects, very much like the adrenal glands can, and then it becomes dysfunctional. As a result, your cortisol, thyroxine and testosterone/oestrogen can become low.

The symptoms are very similar to those with adrenal insufficiency. Other symptoms that may occur are headache and visual changes. The headache is often quite severe, painkillers may not help and it is often worse at the front of the head and when leaning forward. The visual disturbance may be double vision or tunnel vision and may occur with eye pain.

Should you experience any of these symptoms please call The Clatterbridge Cancer Centre Hotline for advice on **0800 169 5555.**

Cortisol when you are unwell

Cortisol is essential for life and the body produces extra cortisol during times of stress, for example, when you have a fever, when you have an infection, when you undergo surgery or are hurt in an accident. If your adrenal gland is not producing enough cortisol, your body may not be able to cope with this added stress, which can be life threatening. This is known as an adrenal crisis and is a medical emergency. Signs of adrenal crisis include low blood pressure, abdominal pain, vomiting and nausea, severely abnormal salt levels in the blood and sometimes fever and confusion.

You will have been given a Steroid Alert Card that has the advice below and the number to contact us on – please carry this with you at all times.

If you feel unwell in any way, please contact us on the emergency number on your immunotherapy alert card.

How is adrenal insufficiency diagnosed?

Adrenal insufficiency can be quite difficult to diagnose due to the unspecific nature of its symptoms. This can occur any time after receiving immunotherapy. Therefore, if you feel fatigued or unwell in any way, contact the cancer centre for advice. The doctors and nurses will carry out a number of blood tests (cortisol/ACTH) including one that they may do at 9am in the morning (9am cortisol) as this is the most accurate time to do it. You do not need

to fast for the 9am test. Most of the time the diagnosis can be made with blood tests but you may also have an ultrasound scan.

A short synacthen test may also be performed to confirm the diagnosis. This tests your adrenal glands response to stimulation from a synthetic form of the adrenal stimulating hormone (ACTH) that you normally produce naturally. The ACTH hormone stimulates the adrenal gland to produce cortisol. When carrying out this test, a baseline blood sample is drawn, before injecting a dose of ACTH, followed by drawing a second blood sample 30-60 mins after this injection. If you are taking hydrocortisone or prednisolone, you will be asked not to take the tablets on the morning of the test but can and should take them the day before as normal. You should then take that day's first dose after the second blood test. If you are taking steroids more than once a day, you can then take the tablets as normal. If you are taking dexamethasone, you can carry on your tablets as normal with no need to delay for the test.

How is pituitary insufficiency diagnosed?

The same blood tests will be undertaken when you first get to hospital as in the case of adrenal insufficiency. You may also have an MRI of your head. It is very rare to require a short synacthen test.

How is adrenal insufficiency treated?

Once diagnosed with adrenal insufficiency, patients will need to take daily medications for the rest of their lives. Immunotherapy induced adrenal insufficiency is usually irreversible. Treatment is typically with corticosteroids (e.g. hydrocortisone), which aim to replace the body's natural cortisol and in some cases mineralocorticoids (e.g. fludrocortisone) to replace the body's natural aldosterone.

Hydrocortisone is the treatment of choice as it closely mimics the body's natural cortisol release and is absorbed from the body quicker than other corticosteroids. Hydrocortisone has to be taken three times a day for this reason. Dexamethasone or/prednisolone can also be used but are less common.

How is pituitary insufficiency treated?

Because the main issue with pituitary insufficiency is also low cortisol, the treatment is very similar. If you have severe headache or visual changes or the MRI shows any evidence of inflammation, then you may be commenced on methylprednisolone, which is given into the vein, followed by tablet prednisolone before starting hydrocortisone but you will end up on the same hydrocortisone doses as are given for adrenal insufficiency. Because the other hormones are also affected, then it is likely you will start on levothyroxine to treat the low thyroid hormone levels and gentlemen will often be started on testosterone replacement. We do not routinely replace oestrogen/progesterone.

How should you take your medications?

Hydrocortisone tablets are taken in two or three divided doses, throughout the day. These are typically split into the higher dose in the morning, and lower doses at noon and/or evening dose. Usual doses are 20mg in the morning followed by 10mg in the afternoon and evening OR 10mg in the morning followed by 5mg in the afternoon and evening. It is common to be started on the higher dose and then dropped to the lower dose after you have been on hydrocortisone for two weeks. It is important to keep the timings of your doses consistent to help match the body's natural cortisol release pattern. Your evening dose should be taken no later than 6pm, or 4 hours before going to sleep to minimise sleep disturbance.

YOU MUST NOT STOP YOUR STERIODS UNLESS EXPLICITLY TOLD TO DO SO. PLEASE ALWAYS ENSURE YOU HAVE A SUFFICIENT SUPPLY FOR WEEKENDS AND HOLIDAYS.

Getting you to your correct dose may take some time and may be adjusted based on your symptoms and blood test results. Your dose may also need further correction if the adrenal gland continues to decline in its production of cortisol and aldosterone.

Most patients are advised to take steroid medications with food. However, most patients with adrenal insufficiency can take their medication first thing in the morning on an empty stomach with

just water. This is because you are taking a smaller daily dose of steroid compared to patients taking steroids for other steroid-dependent conditions. This also means the steroid starts working in your body sooner, rather than waiting until after your breakfast. If you are suffering from indigestion from your steroid medication, switching to swallowing the tablets with milk or a milk substitute, for example, soya or rice milk will usually resolve the issue.

Hydrocortisone is a much less potent steroid than prednisolone or dexamethasone and therefore can be taken long term. The side effects are minimal as the dose you are on is essentially replacing what you used to produce naturally at a very similar level.

Please speak to your pharmacist or doctor if you have concerns over the side effects of these medications. Further information on side effects can be found in your patient information leaflet, which you will have received with your medication.

If you are prescribed levothyroxine, the tablets are taken once a day and you will have blood tests to monitor whether you are taking enough replacement, so the dose may change over time. These tablets are to be taken on an empty stomach, approximately 30 minutes before your breakfast, other medications and caffeine-containing liquids.

Testosterone can be given as an injection or a gel that is rubbed on the skin. If needed, it is likely you will be given the gel to start with. Please ensure you follow the administration instructions

detailed in the patient information leaflet for these medications. Your testosterone levels will be checked via a blood test.

Both adrenal and pituitary insufficiency is usually permanent, so please do not discontinue these medications unless explicitly told to do so.

Special circumstances

If you are a shift worker: medicines should be taken in line with your sleeping pattern. If you work night shifts, the first dose should be taken upon waking and the final dose at least four hours before going to sleep, even if this is in the morning.

Further information on a range of topics, including exercise, diet, travelling, managing adrenal crisis and pregnancy can be found on the Addison's Disease Self-Help Group website (www.addisons.org.uk).

Monitoring

You will remain under the care of your oncologist whilst you are receiving treatment for your cancer. However, your adrenal/pituitary dysfunction will be managed in collaboration with your GP and you may also be referred to see an endocrinologist (a gland specialist).

You should also monitor your own health and be alert for signs of illness when you may need to adjust your daily steroid medications. During your cancer treatment, and for six months after, please contact our 24-hour Clatterbridge Cancer Centre

Hotline on **0800 169 5555**. Please report any side effects you experience if you are on steroids as they may be signs of under or over treatment with your medications. You may find it useful to keep a diary and recording any important health issues or changes.

Please read and carry your steroid alert card with you at all times. It is also worthwhile keeping a picture of this and your immunotherapy alert card on your mobile phone if you have one. This is to be shown to any health care professional that you may see. If you are admitted to hospital, please inform medical staff immediately that you have adrenal insufficiency as you may need extra steroid medication. It is also recommended that you obtain a MedicAlert tag to alert people in an emergency of your condition; for example, it could state "adrenal insufficiency, steroid dependent". These can be purchased on the Addisons Disease Self-Help group website.

'Sick day' rules

As discussed earlier, your body will normally produce extra cortisol during periods of stress. Therefore, it is essential that you adhere to the following rules to ensure you increase your steroids enough to replicate this during times of sickness/significant stress (the table below explains which conditions apply).

It is important that you do not run out of your tablets and that you always have **extra supply** of your hydrocortisone tablets should you need them. Some patients will also have hydrocortisone

injections at home that they, or a family member, can administer during periods of severe diarrhoea/vomiting or trauma although this is not given out as standard. Please contact The Clatterbridge Cancer Centre hotline if you become unwell and indicate whether you have been able to take and keep down your tablets.

If you are not well with a fever that requires bed rest and/or antibiotics please **DOUBLE** your daily dose of steroid. For example, if you take 10mg in the morning, 5mg at noon and 5mg in the evening, you need to increase this to 20mg in the morning, 10mg at noon and 10mg in the evening whilst you are unwell. Further information can be found in the table below:

Illness or stress situation	Increase of usual dose	For how long?	Is this an emergency, or when do I seek help?
Cold with no fever	None necessary		
Fever, flu, infection	Double	For duration of fever	See GP if still unwell after 48 hours
Vomiting- more than once. Also diarrhoea and severe illness	Take extra dose immediately at onset of vomiting. Emergency 100mg injection if extra dose of 10-20mg tablets cannot be kept down.	Resume on usual dose once stable after medical intervention.	Phone GP, or go to A&E. If you have injection at home, you, or a relative or GP can administer this. Also an anti-sickness injection or tablet may be needed.

Surgical procedures	Minor (e.g. tooth extraction) 20mg hydrocortisone before procedure. Small operation (e.g. hernia repair) 100mg injection every 6 hours for 24hours. Major operations (e.g abdomen/chest) 100mg injection or intravenous every 6 hours for 72 hours.	Resume on usual dose immediately after. Reduce rapidly on usual dose.	Tell the anaesthetist and surgeon that you take hydrocortisone before the operation.
Severe shock (e.g. bereavement or road traffic accident)	100mg injection, or take 20mg as tablets if able.	See GP or hospital for further advice.	Sudden and severe shock may be classed an emergency - seek medical attention if in doubt.
General stress e.g. exams, etc.	Not usually required.		Ask GP if concerned.
Long haul flight over 12 hours	Double usual dose on day of flight.	One double dose should suffice.	

What will happen with my immunotherapy treatment?

Whilst both of these side effects are serious and need to be managed urgently, the development of adrenal or pituitary insufficiency rarely means we have to stop treatment for your cancer with immunotherapy. It is important to make sure you recover from the symptoms that occur at the point of diagnosis and that your hormones are sufficiently replaced, but once this has been addressed, immunotherapy is restarted in the vast majority of cases.

Patient support groups

Addison's Disease Self-Help Group

Web: www.addisons.org.uk

Pituitary Foundation

Web: www.pituitary.org.uk

You and your hormones

Web: www.youandyourhormones.info

Some of the information used in this information leaflet has been reproduced with thanks to the Society of Endocrinology and the Pituitary Foundation.

How we produce our information

All of our leaflets are produced by staff at The Clatterbridge Cancer Centre and this information is not sponsored or influenced in any way. Every effort is made to ensure that the information included in this leaflet is accurate and complete and we hope that it will add to any professional advice you have had. All our leaflets are evidence based where appropriate and they are regularly reviewed and updated. If you are concerned about your health in any way, you should consult your healthcare team.

We rely on a number of sources to gather evidence for our information. All of our information is in line with accepted national or international guidelines where possible. Where no guidelines exist, we rely on other reliable sources such as systematic reviews, published clinical trials data or a consensus review of experts. We also use medical textbooks, journals and government publications.

References for this leaflet can be obtained by telephoning 0151 556 5570.

If you need this leaflet in large print, Braille, audio or different language, please call 0151 556 5570.

If you have a comment, concern, compliment or complaint, please call 0151 556 5203.

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