

Oncology Pharmacy Newsletter

The Oncology Pharmacy Newsletter is publication dedicated to providing useful information for the staff treating patients who come to the Oncology Outpatient Pavilion.

We welcome questions and requests for topics.

References available upon

Over how long do I infuse Carfilzomib?

This issue has created some confusion recently, and the answer is, "It varies".

Carfilzomib (Kyprolis®) was originally approved at first cycle doses of 20mg/m² followed by cycles of 27mg/m², to infuse over 10 minutes, on days 1, 2, 8, 9, 15, & 16 of a 28 day cycle.

More recent studies have led to the development of a 20mg/m² on day 1 and 2, of the first cycle only, followed by 56mg/m² doses for the remaining days that infuses Carfilzomib over 30 minutes, even for the 20mg dose. So, follow the protocol.

Rasburicase (Elitek®)

Uric acid is one of the many electrolyte and protein waste products that increase in the bloodstream as a result of tumor lysis syndrome when cellular materials are released following rapid cell death in patients with high tumor burdens. Tumor lysis syndrome can lead to renal failure and death if not treated.

Hydration and diuresis are first line therapies for tumor lysis syndrome. Allopurinol may be used preventatively to try to block the formation of uric acid, but when the uric acid load becomes excessive, rasburicase can enable more rapid clearance of this waste product, reducing the risks of kidney damage or death.

Rasburicase is indicated for the treatment of hyperuricemia resulting from malignancy or the treatment of a malignancy. It is a recombinant urate oxidase enzyme that breaks down the uric acid present in the bloodstream into a more soluble waste product, allantoin, that is then readily excreted by the kidneys. Normal uric acid levels in males are 2-8mg/dL, and for females are 2-7.5mg/dL.

Original dosing regimens for rasburicase were weight based, but more recently several studies have demonstrated efficacy with smaller standardized doses. Our current Pharmacy and Therapeutics approved dosing regimen is rasburicase 3mg once, in 50ml NS infused over 30 minutes. Most patient's will experience a decrease in the uric acid levels within 72 hours. If the uric acid level does not fall, a 3mg dose may be repeated as soon as 24 hours later. Patients with very high uric acid levels could receive 6mg as their initial dose. These regimens have been demonstrated to be equally effective as and less expensive than the original weight based dosing regimens.

Rasburicase is contraindicated in patients with G6PD-deficiency, history of severe hypersensitivity, or methemoglobinemia while on rasburicase. Severe hypersensitivity reactions may occur in 4% of patients. Common adverse reactions include peripheral edema, headache, anxiety, rash, nausea, vomiting, constipation, diarrhea, pain (abdominal or nasopharyngeal), elevated LFTs, and fever.

Blood samples for uric acid levels must be drawn in pre-chilled heparinized tubes, placed in ice, and delivered immediately to the lab, and assayed within 4 hours, or the uric acid may degrade due to the action of rasburicase in the sample.

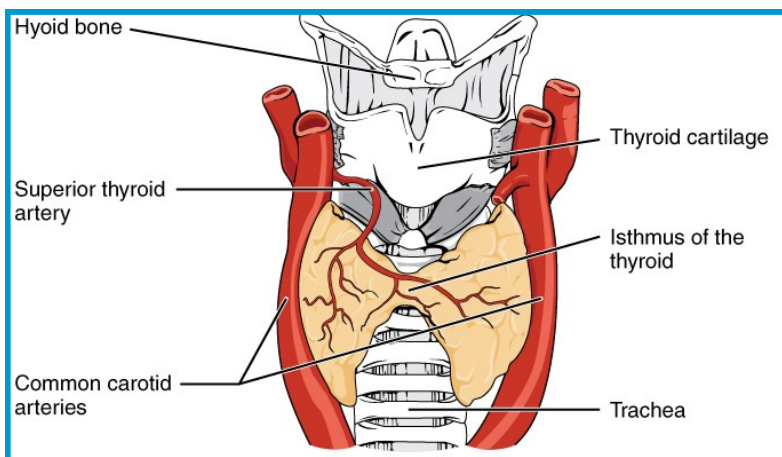
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Thyroid Testing in Oncology Patients

Margaret Cruz, UConn PharmD Candidate 2016

Introduction

Many patients with cancer present with new or chronic thyroid issues.¹ Concurrent hypothyroidism and hyperthyroidism are associated with symptoms that negatively affect the patient's quality of life, and can interfere with the ability to respond to treatment. Therefore proper monitoring of thyroid function is necessary to optimize outcomes and improve patient's overall quality of life.¹ Healthcare providers need to be aware of the signs and symptoms of thyroid dysfunction, the types of tests used to diagnose thyroid disorders, and the common cancer therapies that may cause thyroid disorders.



Thyroid Function

The thyroid is the endocrine gland responsible for releasing thyroid hormones thyroxine or tetraiodothyronine (T4) and triiodothyronine (T3).^{2,3} T4 and T3 primarily regulate metabolism, but also affect muscle strength, temperature regulation, heart rate, brain development, weight, skin dryness, and nervous system functions.^{1,2,4} These hormones are released when the anterior pituitary gland releases thyroid stimulating hormone (TSH) and the overall process is highly regulated by negative feedback inhibition via the hypothalamic-pituitary-thyroid axis.³ The disruption of this axis by tumors, medications, autoimmune disease, etc. results in patients having abnormal hormone levels and suffering associated symptoms (see Table 1).

Hypothyroidism is most commonly caused by medications, previous radiation exposure, thyroid surgery, hyperthyroid treatment, and autoimmune disease. Less common causes include pregnancy, iodine deficiency, pituitary disorders, and congenital thyroid disease. Hyperthyroidism is a condition in which the body over produces thyroid hormones and is caused primarily by Grave's disease, toxic adenomas, Plummer's disease, and thyroiditis.

Chemotherapy agents known to exacerbate thyroid dysfunction are listed in Table 2.¹

Table 1. Symptoms of Thyroid Dysfunction³

Common Symptoms of Thyroid Disorders	
<i>Hyperthyroidism</i>	<i>Hypothyroidism</i>
Diarrhea	Brittle, dry hair
Hair loss	Constipation
Hot flashes	Dry skin
Sweating	General loss of energy
Trembling	Tiredness
Weight loss	Weight gain

Thyroid Testing in Oncology Patients, continued:

Table 2. Chemotherapy Agents Known to Cause Thyroid Dysfunction

Therapy	Notable Examples	Dysfunction
Radiation ¹		Hypothyroidism
Tyrosine Kinase Inhibitors ¹	Sunitinib (Sutent) ² Sorafenib (Nexavar) ² Imatinib (Gleevec) ² Dasatinib (Sprycel) ² Nilotinib (Tasigna) ² Axitinib (Inlyta) ²	Hypothyroidism* Hypothyroidism Hypothyroidism Hyper/Hypothyroidism/Thyroiditis Hyper/Hypothyroidism Hyper/Hypothyroidism
Monoclonal Antibodies	Ipilimumab (Yervoy) ¹¹ Nivolumab (Opdivo) ¹¹ Pembrolizumab (Keytruda) ¹¹	Hypothyroidism Hyper/hypothyroidism Hyper/hypothyroidism
Cytokines	Interferon-Alpha ²	Hyper/Hypothyroidism

*Cases of hyperthyroidism, followed by hypothyroidism have been reported

Monitoring Recommendations

The United States Preventative Services Task Force (USPSTF) concluded they have insufficient evidence to recommend for or against routine screening for thyroid disease in asymptomatic, non-pregnant adults.⁵ However, patients who experience symptoms commonly associated with hypo- or hyperthyroidism should be evaluated with a TSH level. If abnormal values are reported, additional thyroid tests may be ordered depending on result, signs/symptoms, and likely causes. Table 3 provides an overview of the current tests available, basic result interpretation, and the UConn Health's reference for normal ranges.⁶⁻⁸

For chemotherapeutic agents known to cause thyroid dysfunction (Table 2) TSH should also be monitored every 4 weeks for 4 months, and then once every 2-3 months if patients do not have pre-existing levothyroxine therapy. If they do, it is recommended to test baseline, every 4 weeks until levels and levothyroxine dose is stable, and then once every 2 months. Recommendation sometimes change based published literature, so using a drug resource like Lexicomp for monitoring frequency is recommended. Additionally, if patients report any of the previously listed symptoms (Table 1), it would be important to order a follow-up TSH to delineate the cause at that time.

Additional Test Interpretation: It should be noted that not all abnormal values are indicative of thyroid disease, and certain tests require further interpretation when evaluating results.

Free Thyroid Index (FTI):

This test has been provided for completeness, however, it has since been replaced by the FT4 test and it is not utilized at UConn Health. It is calculated by dividing the free thyroxine (FT4) by thyroid binding capacity.⁹

Thyroglobulin Antibody (TGA):

This test should be interpreted with TSH levels, radioiodine ablation status, and serial thyroglobulin measurements. The positive predictive value for this test in antithyrotic patients is modest. If apparent concentration is <1ng/mL the sample should be re-measured with mass spectrometry. If a patient is TGA positive, it is preferred to re-test with mass spectrometry due to the high incidence of underestimation.⁸ Patients who have levels >10ng/mL have at least a 25% risk of clinically detectable residual/recurrent disease.⁸ The following values correspond to risk of developing clinically detectable recurrent papillary/follicular thyroid

Thyroid Testing in Oncology Patients, continued:

cancer:

TgAb <0.5ng/mL: Minimal Risk

TgAb 0.5-2.0ng/mL: Low Risk

TgAb 2.1-9.9ng/mL: Increased Risk

Table 3. Thyroid Tests⁶⁻⁸

Test Name	Test Type	Normal Values	Result Interpretation	Comment(s)
TSH	Blood	0.35-4.94U/mL	High: Primary Hypothyroidism Low: Hyperthyroidism/ Secondary Hypothyroidism*	Best way to initially test thyroid function
T₄ FT₄ FTI	Blood	4.87-11.72ug/dL 20-39yo: 0.61-1.82ng/dL 40-59yo: 0.5-1.39ng/dL 60-79yo: 0.6-1.89ng/dL >79yo: 0.66-1.50ng/dL Pregnancy: 1 st Trimester: 0.66-1.27ng/dL 2 nd Trimester: 0.60-1.15ng/dL 3 rd Trimester: 0.53-1.09ng/dL 1-4.3U	High: Hyperthyroidism Low: Primary Hypothyroidism/ Secondary Hypothyroidism	FT ₄ : Most important to test how the thyroid is functioning
T₃	Blood	48-178ng/dL	High: Hyperthyroidism Low: Hypothyroidism	More useful in determining hyperthyroidism
Thyroid Ab TGAb TPO	Blood	 0.0-4.0IU/mL 0.0-9.0IU/mL	Positive/High: Possible recurrent disease or residual disease Positive TPO: Autoimmune thyroid disease	TGAb: Useful to monitor patients who had surgical resection following thyroid cancer Anti-TPO: Help indicate the cause of thyroid problems
RAIU	Non-Blood	<80 ng/dL	80-250ng/dL: Hyperthyroidism >250ng/dL: Iodine overload	Patients swallow a liquid or capsule containing radioactive iodine

*Secondary hypothyroidism: Abnormality in thyroid function due to pituitary gland

Ab, Antibody; FT₄, Free T₄; FTI: Free thyroxine index; RAIU, Radioactive iodine uptake; TGAb, Thyroglobulin antibody; TPO, Thyroid peroxidase antibody.

Thyroid Testing in Oncology Patients, continued:

Thyroid Peroxidase Antibody (TPO):

Values >9 IU/mL are often associated with autoimmune disease.⁷ Patients who are asymptomatic and present with these values are at increased risk of developing other autoimmune disorders and have a higher annual risk of developing hypothyroidism (4.3% vs. 2.1%).¹⁰

Special Considerations:

- ◆ TGAb and TPO are tests that cannot be evaluated in-house and must be sent to ARUP and Mayo. Patients should be made aware that these results may take a longer amount of time to come back.
- ◆ A recent CT with contrast can affect the overall reliability of the radioactive iodine uptake (RAIU) test. Try to administer and evaluate tests >6 weeks after a CT.¹
- ◆ Patients should not take any multivitamin or dietary supplement containing biotin or vitamin B7 12 hours before testing T4, T3, or FTI.⁹

References:

¹Hartmann, K. Thyroid disorders in the oncology patient. J Adv Pract Oncol. 2015. 6(2). 99-106.

²National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD. Thyroid Tests. [Updated May 2014; Accessed February 8, 2016]. <http://www.niddk.nih.gov/health-information/health-topics/diagnostic-tests/thyroid-tests/Pages/default.aspx>

³National Center for Biotechnology Information. Bethesda, MD. How does the thyroid work? [Updated January 7, 2015; Accessed February 8, 2016]. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072572/>

⁴Thyroid function tests. Chemocare. <http://chemocare.com/chemotherapy/side-effects/thyroid-function-tests.aspx>. Accessed: February 8, 2016.

⁵Final Recommendation Statement: Thyroid Dysfunction: Screening. U.S. Preventive Services Task Force. March 2015. <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/thyroid-dysfunction-screening>

⁶American Thyroid Association. Falls Church, VA. Thyroid Function Tests. [Updated 2014, Accessed February 8, 2016]. http://www.thyroid.org/wp-content/uploads/patients/brochures/FunctionTests_brochure.pdf

⁷McAuley, D. Common Laboratory Values. Global RPh. [Updated November 11, 2015; Accessed February 8, 2016]. http://www.globalrph.com/labs_t.htm#Thyroid

⁸Mayo Clinic. Rochester, MN. Test ID: Thyroglobulin. [Accessed February 8, 2016]. <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/62936>

⁹Mayo Clinic. Rochester, MN. Test ID: Free Thyroxine Index. [Accessed February 8, 2016]. <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/62583>

¹⁰Mayo Clinic. Rochester, MN. Test ID: TPO. [Accessed February 8, 2016]. <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/81765>

¹¹Lexicomp accessed 4/1/2016

References for Rasburicase:

Cairo, MS and Bishop, M, Tumour lysis syndrome: new therapeutic strategies and classification
22 JUL 2004

Lexicomp Accessed 3/22/2016

Coutsouvelis J, Wiseman M et al. Effectiveness of a single fixed dose of rasburicase 3 mg in the management of tumour lysis syndrome. British Journal of Clinical Pharmacology 2013; 75(2):550-553

Hutcherson DA, Gammon DC, et al. Reduced-dose rasburicase in the treatment of adults with hyperuricemia associated with malignancy. Pharmacotherapy 2006; 26(2):242-7.

Trifilio S, Gordon L et al. Reduced-dose rasburicase in adult cancer patients with hyperuricemia. Bone Marrow Transplant 2006; 37:997.

Dinnel, J et al., Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy; Core Evid. 2015; 10: 23-38.

November 2015, Pharmacy and Therapeutics Committee minutes.

Suggestions for topics, questions, and comments are welcome! Just reply to sender of this newsletter or email:

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