BC Cancer Clinical Pharmacy Guide

Liver Function and Associated Laboratory Tests

Contents

Introduction

Liver function tests (LFTs) can be difficult to interpret because there is no readily available laboratory test that quantitatively measures liver function. Instead, the serum tests available to estimate liver function will assess:

- Hepatocellular injury - alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- The liver's ability to synthesize - albumin and prothrombin time (PT)
- The presence of cholestasis - alkaline phosphatase (ALP), bilirubin and gamma glutamyl transpeptidase (GGT)

The correlation between these tests and hepatic dysfunction may be limited.

Most liver function tests are not specific to one organ and elevations can be the result of a variety of disease processes. Comparing the pattern of abnormalities of the liver function tests and the patient's overall clinical picture is more accurate than any of the individual tests. Recognition of these abnormal patterns will help to determine the etiology of the abnormality.

For example:

- Elevations in ALT and AST can be caused by alcoholic or nonalcoholic fatty liver disease, thyroid disorders, anorexia and common OTC medications such as acetaminophen and NSAIDs.
- Mildly elevated ALP levels with normal ALT and AST values may be seen in pregnancy.
- Mildly elevated ALP and bilirubin levels with markedly elevated ALT and AST values may be an indication of hepatocellular disease.

See the *Lab Test Interpretation Table*, located below this document on the Clinical Pharmacy Guide webpage, for examples of normal values and interpretation tips.

Bilirubin

Bilirubin is primarily a breakdown product of red blood cells and is derived from hemoglobin.

Two forms are available:

1) indirect or unconjugated bilirubin is fat soluble, bound to albumin (it is not filtered by the glomerulus and not present in urine), and transported to the liver

2) direct or conjugated bilirubin is conjugated by the liver into a water soluble form (can be found in the urine) and is primarily excreted into the bile

The total bilirubin is the sum of the two and tends not to be a sensitive indicator of hepatic function; it is more a measure of excretion than metabolism.

Most BC Cancer protocols refer to total bilirubin.

An increase in the total bilirubin may indicate:

- increased bilirubin formation (i.e., hemolysis)
- reduced rate of bilirubin conjugation (i.e., Gilbert's syndrome)
- impaired secretion into bile (i.e., hepatobiliary disease)

In the case of impaired secretion, the dosage of drugs that are primarily excreted via the biliary system should be reduced. For example, in the BRAVAC protocol, when bilirubin levels rise to between 25 to 50 micromol/L, the recommendation is to reduce the doxorubicin dose by 50%; when bilirubin rises between 51 to 85 micromol/L, the recommendation is to reduce doxorubicin to 25% dose. At a bilirubin level greater than 85 micromol/L, treatment should be held. Table 3 provides examples of drugs excreted in the bile that that may require dose reductions if total bilirubin is elevated.

Table 3: Examples of Cancer Drugs Excreted by the Biliary System		
DOXOrubicin	irinotecan	sorafenib
epirubicin	methotrexate	sunitinib
etoposide	mitoXANTRONE	vinblastine
5-fluorouracil	PACLitaxel	vincristine
imatinib		vinorelbine

Alkaline Phosphatase (Alk Phos)

Circulating alkaline phosphatase (ALP) is derived primarily from the liver and bone (~80%), but is also found in the intestine, kidneys, placenta, and leukocytes. ALP refers to a group of enzymes with unknown function. This test is considered nonspecific but can provide useful information in conjunction with other LFTs.

Elevated ALP may indicate cholestatic disease, hepatic injury, and extrahepatic processes (e.g., malignancies, healing fractures, bone metastases).

The dose of docetaxel in the BRAVDOC protocol may be reduced if ALP is elevated, but only if ALT is also elevated.

Alanine Aminotransferase (ALT)

Alanine aminotransferase (ALT) is found primarily in the liver but also in the skeletal muscle, heart and kidneys. It is more abundant than aspartate aminotransferase (AST) in hepatic tissue; therefore ALT is a more liver-specific enzyme. With acute hepatic injury, initial elevation of AST is greater than that of ALT. However, elevation of ALT eventually exceeds that of AST which is metabolized more quickly. ALT can also be elevated in patients with muscular disease, myocardial injury, and renal infarction.

The dose of docetaxel and paclitaxel may be reduced due to elevated serum ALT. The BRAVDOC protocol is a good example of a treatment protocol summary where liver function tests (ALP and ALT) are used in combination to determine the dose reduction of a drug.

The BRAVTAX protocol recommends paclitaxel dose modifications while accounting for the presence of liver metastases. With the presence of liver metastases, a paclitaxel dose reduction is suggested if ALT is greater than or equal to 5 times the upper limit of normal (ULN). Without the presence of liver metastases, a paclitaxel dose reduction is suggested if ALT is greater than 2 × ULN.

CNTEMOZ (temozolomide) is another example of a protocol with dose reductions based on ALT levels.

Aspartate Aminotransferase (AST)

Aspartate aminotransferase (AST) is found in cardiac and skeletal muscle, as well as the liver, kidney, and pancreas. It is more specific to cardiac and skeletal muscle and is often monitored with ALT. It is an optional test and is not done routinely as a part of the liver panel tests. It can be ordered if required at the physician's discretion.

With the exception of some Clinical Trials, BC Cancer has eliminated AST from protocols and PPOs and ALT is preferentially ordered.

Lactic Dehydrogenase (LDH)

Lactic dehydrogenase (LDH) is a glycolytic enzyme that catalyzes the conversion of lactate to

pyruvate. Although present in most tissues, higher concentrations of LDH are found in the heart, kidney, liver, and skeletal muscle. An elevated serum concentration can be caused by disease in many different organs, limiting its diagnostic usefulness. There are five isoenzymes of LDH which offers diagnostic specificity. Elevated isoenzyme LDH-5 is associated with liver disease.

In BC Cancer protocols, LDH is not usually used as a basis for dose modifications, but may be monitored to establish protocol eligibility, assess tumour burden, or as a baseline test prior to treatment.

LDH can be elevated in some solid and hematologic malignancies such as testicular cancer, lymphomas, leukemias, as well as tumour lysis syndrome (TLS). LDH is also a prognostic factor in lymphoma and elevated LDH values may be associated with disease progression and can be useful when considering further treatment.

Elevated baseline LDH levels (e.g., greater than 2 x ULN) are associated with increased tumour burden and therefore greater risk of TLS in patients with aggressive hematologic cancers.

LDH can also increase due to bone metastases.