



Liver Function and Associated Laboratory Tests

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

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

Most liver tests are not specific to one organ; therefore, elevations can be the result of a variety of disease processes. For example, elevations in AST can be caused by liver disease, thyroid disorders, anorexia, etc. Comparing abnormal tests to other lab tests and the patient's clinical picture can help determine the cause. For example, mildly elevated Alk phos levels with normal ALT and AST values may be seen in pregnancy. However, mildly elevated Alk phos 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, for 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, which is fat soluble, is bound to albumin, and transported to the liver; and 2) direct or conjugated, which is conjugated by the liver into a water soluble form 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. The BC Cancer protocols refer to total bilirubin.

An increase in the total bilirubin may indicate: (1) increased bilirubin formation (i.e., hemolysis), (2) reduced rate of bilirubin conjugation (i.e., Gilbert's syndrome), and (3) impaired secretion into bile (i.e., hepatobiliary disease). In

the latter scenario, the dosage of drugs that are primarily excreted via the biliary system should be reduced. For example, in the BRAVAC protocol, when bilirubin rises to 25 micromol/L, DOXOrubicin is reduced by 50%; when bilirubin rises over 50 micromol/L, DOXOrubicin is reduced to 25%. At a bilirubin level of over 85 micromol/L, treatment is 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	imatinib	PACLitaxel
epirubicin	irinotecan	vinBLAStine
etoposide	methotrexate	vinCRISStine
5-fluorouracil	mitoXANTRONE	vinorelbine

Alkaline Phosphatase (Alk Phos)

Circulating alkaline phosphatase (Alk phos) is derived primarily from the liver and bone (~80%), but is also found in the intestine, kidneys, placenta, and leukocytes. Alk phos 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 Alk phos 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 Alk phos is elevated, but only if AST or ALT is also elevated.

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.

The dose of DOCEtaxel and PACLitaxel may be reduced for elevated AST, as outlined in BRAVDOC and BRAVTAX protocols. The BRAVTAX protocol accounts for the presence of liver metastases by recommending a PACLitaxel dose reduction at AST greater than or equal to 5 times the upper limit of normal (ULN). Without liver metastases, the PACLitaxel dose is reduced at AST greater than $2 \times$ ULN. CNTEMOZ (temozolomide) is another example of a protocol with dose reductions based on AST.

Alanine Aminotransferase (ALT)

Alanine aminotransferase (ALT) is often monitored in combination with AST. ALT is more abundant than AST in hepatic tissue; therefore ALT is a more liver-specific enzyme. It can also be elevated in patients with muscular disease, myocardial injury, and renal infarction.

As with AST, 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 are used in combination to determine the dose reduction of a drug.

Lactate Dehydrogenase (LDH)

Lactate 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 or as a baseline test prior to treatment. It is also a prognostic factor in lymphoma and



may be monitored for this reason. Elevated LDH values may be associated with disease progression and can be useful when considering further treatment.