

Clinical Chemistry Question and Answer

Edited by Alan H.B. Wu and Fred S. Apple

Answered by: Edward Stelow, M.D., Pathology Resident,
Hennepin County Medical Center, Minneapolis, MN USA.

Q What is the use of alpha-fetoprotein as a tumor marker?

A Alpha-fetoprotein (AFP) is a protein that is synthesized mostly in fetal yolk sac cells and fetal hepatocytes (and, to a lesser extent, other cells of the fetal gastrointestinal tract).^{3,5} It can comprise up to one-third of the total protein in fetal serum during the second trimester.⁵ While its function is not fully understood, it is thought to have a function analogous to that of albumin in the adult, and perhaps has an immunosuppressive role.⁵ After birth, AFP concentrations generally fall into the normal adult range by one year of age (< 10 g/l).⁵ Concentrations can be increased during pregnancy and hepatic injury.⁵ It is not surprising that as a tumor marker, AFP is used in both germ cell tumors and hepatocellular carcinoma (HCC).^{1,6} It can be increased in other tumors such as pancreatic carcinoma, but lacks both sensitivity and specificity.⁵

As nonseminomatous germ cell tumors (NSGCTs) can show yolk sac differentiation, these tumors have been shown often to have increased AFP concentrations.^{1,2,3,5} As the tumors are often small at the time of diagnosis and because NSGCTs can show varying differentiation, AFP has not been shown to be useful as a screening marker in this disease.³ When precise diagnosis of a tumor type is difficult, increased serum concentrations of AFP can be helpful inasmuch as they indicate yolk sac differentiation.¹ This is especially true when this information is coupled with human chorionic gonadotropin serum concentrations, a protein that can be increased with chorionic differentiation.^{1,2,3,5}

Serum concentrations are also useful in NSGCTs as regards to prognosis and staging. Multiple studies have shown an extremely increased AFP concentration to be an independent risk factor for poor prognosis.^{1,2} Generally these studies require an AFP concentration > 1000 g/l to indicate an extremely increased concentration.¹ Persistent increased concentrations following surgical treatment indicate metastatic or residual disease and are helpful with staging the disease when no residual tumor can be found by other means.¹

During and following chemotherapy and/or surgery, further monitoring of concentrations has also been shown to be helpful.^{1,2} AFP is cleared by the liver and usually has a half-life of about five days.² It has been shown that increases in half-life following therapy can indicate a poorer prognosis.² This involves difficult calculations and must also take into account the elevated levels that can occur during the first week of therapy, probably secondary to tumor lysis.² Finally, using serum doubling times and concentrations of serum AFP that are indicative of poor prognosis, schemes have been developed that indicate how often to monitor concentrations after thera-

py with the hope of finding the disease before concentrations reach those indicative of a worse prognosis.²

Serum AFP concentrations are also helpful when dealing with hepatocellular carcinoma.^{3,6} It had formerly been shown that 90% of HCC patients had increased concentrations of AFP and that 50% had concentrations that were > 1000 g/l.³ As smaller tumors are detected, these numbers, which demonstrate the sensitivity of the test at various concentrations, will be lower. Some investigators have reported that only 64% of tumors have concentrations > 20 g/l.⁶

By the time HCC becomes clinically evident, the short-term mortality is very high.⁶ At that time, concentrations of AFP will often be extremely increased and the tumor will either be so large as to make surgical resection impossible or will have already metastasized.^{3,6} It is therefore desirable to detect this carcinoma early in its development through screening. Serum AFP concentrations have been shown to be most useful with regards to this tumor.

Hepatocellular carcinoma is a relatively rare tumor in populations that are not at risk, and screenings of entire populations would be too costly.^{4,6} The tumor is much more prevalent in populations with histories of hepatitis and/or cirrhosis, and most screening trials have been conducted in these populations.^{4,6} Higher concentrations of AFP tend to show increased specificity for the disease and decreased sensitivity,³ especially as both hepatitis and cirrhosis can cause increased AFP concentrations.^{3,6} The test is therefore generally combined with radiographic studies, especially ultrasonography.⁴ If only one test is positive, further radiographic studies and needle biopsy can prove helpful.⁴ As a value for screening, centers often use serum AFP concentrations of only > 20 g/l, and in some cases, concentrations of only > 10 g/l.^{4,6} These concentrations are often obtained from patients with hepatitis or cirrhosis, or both, although those patients tend not to have concentrations > 200 g/l.³ Screening has been shown to aid in the diagnosis of small tumors, which tend to have a better prognosis.⁶

REFERENCES

1. Bartlett NL, Freiha FS, Torti FM: Serum markers in germ cell neoplasms. *Hematol Oncol Clin North Am* 1991;5:1245-1260.
2. Bosl GJ, Chaganti RSK: The use of tumor markers in germ cell malignancies. *Hematol Oncol Clin North Am* 1994;8:573-587.
3. Burtis CA, Ashwood ER (ed): *Tietz Textbook of Clinical Chemistry*. Philadelphia, PA, WB Saunders Co., 1994.
4. Ijzermans JNM, Bac DJ: Recent developments in screening, diagnosis and surgical treatment of hepatocellular carcinoma. *Scand J Gastroenterol* 1997;32:50-54.
5. Henry JB (ed): *Clinical Diagnosis and Management by Laboratory Methods*. Philadelphia, PA, WB Saunders Co., 1996.
6. Khakoo SI, Leonie FL, Soni PN, et al: Etiology, screening, and treatment of hepatocellular carcinoma. *Med Clin North Am* 1996;80:1121-1145.

ifcc