ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 261–271

UROLOGIC ONCOLOGY

Seminar article

Current and future biologic markers for disease progression and relapse in testicular germ cell tumors: A review

Timothy A. Masterson, M.D.*, Kevin R. Rice, M.D., Stephen D.W. Beck, M.D.

Department of Urology, Indiana University Medical Center, Indianapolis, IN

Received 18 March 2013; received in revised form 30 April 2013; accepted 15 May 2013

Abstract: Testicular germ cell tumors represent a biologically unique disease process. These tumors are exquisitely sensitive to platinum-based chemotherapy, can be cured with surgical metastasectomy, and are known for the integration of biologic markers to stage and assign risk. Exploring further biologic markers that offer insight into the molecular mechanisms that contribute to disease biology is important. In this review, we attempt to summarize the utility of the current and some future biologic markers for disease monitoring and relapse.

Keywords: Germ cell tumor; Testicular cancer; Biomarkers; Serum tumor markers; Angiogenesis; Epigenetics; Gene profiling

Introduction

Germ cell tumors (GCTs) are comprised of several histologic subtypes, including seminomas and nonseminomas, which arise from both gonadal and extragonadal anatomic sites. Testicular cancer is the most common solid tumor among young men, with incidence rates increasing almost 2-fold over the past 30 years in the United States [1]. Seminomas and nonseminomas have distinctly different biologic characteristics and metastatic potential, with nonseminomas carrying a greater propensity for early spread and a poorer prognosis in advanced stage disease. Clinical and serologic markers of disease have served as key prognostic factors when assessing risk in early and advanced staged patients. GCTs are among a relatively few number of neoplasms where biochemical markers play an important role. In fact, the American Joint Committee on Cancer TNM staging system for GCT is the only such system to incorporate a distinct "S" category for stratifying patients into different stages based on the degree of serum tumor marker (STM) elevation. STM levels in patients with testicular cancer are integral in patient management contributing to diagnosis, staging and risk assessment, evaluation of response to therapy, and detection of relapse. The International Germ Cell Cancer Collaborative Group (IGCCCG) [2] included into the fifth edition of the TNM [3] staging classification 3 STMs: α-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH). A summary of these markers is provided in Table 1.

Although the implementation of these markers for progression has improved our ability to counsel our patients with regard to likely outcomes and risk of relapse, large gaps remain in our ability to reliably exclude patients from unnecessary treatment or implement lifesaving therapies in those destined to fail. In this review, we summarize the utility of current as well as potential future biologic markers for disease relapse. Excluded from this review is any discussion regarding markers incorporated into the molecular and histologic characterization of GCTs during tumorigenesis and pathologic diagnostics.

STM characteristics

AFP

AFP is a single-chain glycoprotein with a molecular weight of 70,000 Da. In the fetus, AFP is a major serum-binding protein produced by the fetal yolk sac, liver, and gastrointestinal tract. The highest concentrations approach 3 g/l during the 12th to 14th weeks of gestation and decline to <40 ng/ml 1 year after birth [4]. The metabolic half-life of AFP is between 5 and 7 days.

AFP is secreted by embryonal cell carcinoma and yolk sac tumor, but not by pure choriocarcinoma or pure

* Corresponding author. Tel.: +131-7-948-7560; fax: +131-7-944-0174.
E-mail address: tamaster@iupui.edu (T.A. Masterson).

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2013.05.012

Table 1
Serum tumor marker summary for testicular germ cell tumors

Marker	Weight (Da)	Half-life	Associated GCT subtype (%)	False negative
AFP	70,000	5–7 d	Yolk sac tumor (90) Embryonal Carcinoma (75)	Liver disease Hereditary persistence of AFP Hepatocellular, lung, pancreatic, colon, and gastric carcinomas
hCG	38,000	24–36 h	Choriocarcinoma (100) Embryonal carcinoma (40–60) Seminoma (10–20)	β subunit of LH cross-reactivity Hypogonadism Marijuana abuse Hepatocellular, breast, pancreatic, gastric, kidney, and bladder carcinomas
LDH	134,000	10–72 h	All GCT (~50)	Liver and congestive heart failure Hemolytic anemia Pancreatitis Collagen vascular disorders Muscular dystrophies
PLAP	60,000–70,000	2–7 d	Seminoma (30–60)	Tobacco abuse

seminoma. Yolk sac tumors appear to be the primary source of AFP with more than 90% of tumors reacting positively to anti-AFP antibody, and in those tumors not demonstrating reactivity to anti-AFP antibody, serum levels are not elevated [5,6]. Falsely elevated AFP values can be seen after treatment in patients with liver disease, hereditary persistence of AFP [7], and several malignancies including hepatocellular carcinoma, lung, pancreatic, colon, and gastric cancers.

hCG

hCG is a glycoprotein with a molecular weight of 38,000 Da composed of α and β subunits. The α subunit of hCG closely resembles the α subunit of other pituitary hormones including luteinizing hormone (LH), follicle-stimulating hormone, and thyroid-stimulating hormone. The β subunit of hCG contains a 24-amino acid C-terminal extension making it antigenically distinct from the other pituitary hormones allowing production of antibodies for the hCG β subunit used in radioimmunoassays [8,9].

During pregnancy, hCG is produced primarily by the syncytiotrophoblastic cells of the placenta and serves to maintain the corpus luteum. Similarly, in GCT, syncytiotrophoblastic cells are responsible for the production of hCG. All patients with choriocarcinoma and 40% to 60% of patients with embryonal cell carcinoma have elevated serum levels of hCG. Approximately 10% to 20% of patients with pure seminoma have elevated serum hCG though the level is typically below 500 U/l. The serum half-life of hCG is between 24 and 36 hours.

For most quantitative hCG assays, the upper limit of normal is between 5 and 10 U/l. Some cross-reactivity with the β subunit of LH may occur resulting in a false-positive test. With the development of more sensitive and specific assays, it has become evident that the pituitary gland is capable of producing hCG [10]. Furthermore, hypogonadism can induce LH as well as hCG production by the pituitary gland [11]. Short course of testosterone replacement suppresses pituitary LH and hCG secretion allowing for a "true" measure of serum hCG of potential germ cell origin [12]. Marijuana use has been attributed to a falsely elevated serum hCG, although conflicting data have been reported [13,14]. Other non-GCTs can produce hCG and include tumors of the liver, pancreas, stomach, breast, kidney, and bladder.

LDH

LDH is a cytoplasmic enzyme with a molecular weight of 134,000 Da found in all living cells. LDH catalyzes the reduction of pyruvate to lactate. Dying and dead cells leak LDH, which can be measured in the serum. As such, there is a direct relationship between tumor burden and LDH levels. LDH measured in the serum is a mixture of 5 isoenzymes each as a tetramer formed by a combination of 2 different subunits encoded by structurally distinct genes, LDHA and LDHB [15]. GCT patients typically express high levels of LDH isoenzyme 1 (LDH-1). However, LDH represents a nonspecific marker for the burden of disease and can be elevated in non-GCT malignancies and conditions of chronic disease, such as liver and congestive heart failure, pancreatitis, hemolytic anemia, collagen vascular disorders, and muscular dystrophies among others. The use of LDH in assessing for GCT relapse has been associated with a positive predictive value and sensitivity of only 13% and 40% in one study, respectively [17]. Therefore, serum LDH levels must be incorporated with other clinical signs when making management decisions concerning GCTs [16,17].

Placental alkaline phosphatase (PLAP)

PLAP is a fetal isoenzyme and is most frequently elevated in patients with seminoma (60%–70%). Serum concentrations of PLAP are increased up to 10-fold in smokers. In a Danish study assessing its value in 236