Guideline Summary

ASCO Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors

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Context

ASCO convened an Expert Panel to consider evidence and craft recommendations on serum tumor markers (STMs) for germ cell tumors (GCTs) in adult males. The recommendations were recently published in *Journal of Clinical Oncology*.¹ In males, most GCTs originate in the testes, accounting for approximately 95% of testicular cancers; however, GCTs occasionally originate extragonadally in the mediastinum or retroperitoneum.

Well-established STMs for guiding management of patients with GCTs include human chorionic gonadotropin (hCG), α -fetoprotein (AFP), and lactate dehydrogenase (LDH). Potential uses of STMs for GCTs may include screening, diagnosis, monitoring during treatment, and post-therapy surveillance. The guideline¹ examines STMs for monitoring or surveillance separately for each histologic GCT subtype: seminoma and nonseminomatous (NS) (including GCTs of mixed histology).

No studies directly compared outcomes of patient management with versus without marker assays. A literature search of MEDLINE and EMBASE identified few prospective studies and no randomized controlled trials; most were retrospective series. For most uses, few studies reported primary outcomes. Thus, Panel recommendations are based primarily on surrogate outcomes, such as rates of relapse in patient subsets with versus without a marker elevation and/or time to detection of relapse.

Clinical Questions and Recommendations

Screening

1. Clinical question. *Are STM assays indicated to screen asymptomatic male adults without current or prior clinical findings suggestive of GCT?*¹

Recommendation 1. The Panel recommends against using STM assays or any other blood tests to screen for GCTs. A summary of key information for STMs is shown in Appendix Table A1 (online only). Incidence and mortality from testis cancer and extragonadal GCTs is low (approximately 400 deaths in the United States annually from testis cancer and fewer from extragonadal GCTs). Thus, it is highly unlikely that screening with STMs or any other tests could decrease mortality or be cost effective for these diseases.

Diagnosis

2. Clinical question. *In the following circumstances, are STM assays indicated to diagnose adults clinically suspected to have GCT?*

2A. *To help determine the need for orchiectomy in patients with a testis abnormality?*

Recommendation 2A. The Panel recommends drawing blood to measure serum AFP and hCG before orchiectomy for all patients suspected of having a testicular GCT to help establish the diagnosis and interpret postorchiectomy levels. However, the Panel recommends against use of STM assay results to guide decision making on need for an orchiectomy. Concentrations in the normal range do not rule out testicular neoplasm or the need for diagnostic orchiectomy.

One reason for measuring STMs preorchiectomy is that seminomas do not produce AFP, and thus a significantly elevated AFP rules out a diagnosis of pure seminoma, regardless of histology. A second is to help determine whether and how quickly STMs decline postorchiectomy. The Panel stressed caution when interpreting borderline elevations because false-positive results are possible (Appendix Table A2; online only).

2B. *To evaluate cancers of unknown primary (CUP) possibly derived from GCT?*

Recommendation 2B. The Panel recommends against using serum AFP and hCG assay results to guide treatment of patients with CUP and indeterminate histology, because evidence is lacking to support this use. Consider treatment with a chemotherapy regimen for disseminated GCT in patients presenting with undifferentiated midline carcinoma even if serum hCG and AFP concentrations are within normal ranges. No analyses have shown statistically significant results for the predictive value of STM in patients with CUP.

2C. *To evaluate patients presenting with metastatic disease and evidence of a testicular, retroperitoneal, or anterior mediastinal primary tumor?*

Recommendation 2C. In rare male patients presenting with testicular, retroperitoneal, or anterior mediastinal primary tumor and whose disease burden has resulted in an urgent need to

start treatment, substantially elevated serum AFP and/or hCG may be considered sufficient for diagnosis of GCT. For such rare, medically unstable patients, treatment need not be delayed until after tissue diagnosis.

In nearly all cases, treatment decisions can and should wait for histopathology results. However, for the rare patient with a disease burden that demands urgent treatment, highly elevated AFP and/or hCG concentrations, together with either a testis mass plus metastatic disease or radiographic evidence of advanced stage cancer with a midline dissemination pattern consistent with GCT, is adequate for diagnosis and chemotherapy.

Caveat on evidence available for questions 3 and 4. Conclusive direct evidence was lacking to compare survival or other health outcomes after treatment decisions made with versus without STM assay results. Consequently, nearly all recommendations on monitoring treatment (I-3 and II-3) or surveillance after treatment (I-4 and II-4) for NSGCT (I-3 and I-4) or seminoma (II-3 and II-4) are based on evidence from secondary outcomes.

Part I: NSGCT

I-3. Clinical question. In adult patients undergoing treatment (or observation) for NSGCT (postorchietomy, for those with testicular tumors), are STM assays indicated for the following uses:

I-3A. To stage patients and predict prognosis before chemotherapy and/or additional surgery?

Recommendation I-3A-1. Although conclusive evidence is lacking, the Panel recommends measuring serum AFP, hCG, and LDH for all patients with testicular NSGCT shortly after orchietomy and before any subsequent treatment. The magnitude of postorchietomy STM elevations is used to stratify risk and select treatment but must be interpreted appropriately. Serial STM measurements may be needed to determine whether STM levels are rising or falling and, if falling, whether the decline approximates the marker's biologic half-life (24 to 36 hours for hCG; 7 days for AFP).

Data on secondary outcomes support using persistent postorchietomy AFP or hCG elevations to identify patients with low-stage NSGCT who would have a relatively high risk of relapse if treated with retroperitoneal lymph node dissection (RPLND) and who are more likely to be cured with systemic chemotherapy. The magnitude of marker elevations contributes to management decisions for patients with metastatic NSGCT. The guideline recommends caution when interpreting marker results, as there are conditions that can lead to false positives (Appendix Table A2). Caution is particularly necessary when increased LDH is unaccompanied by other evidence of disease progression or relapse, such as increased AFP or hCG or abnormal radiographic or physical examination findings.

Recommendation I-3A-2. Although conclusive evidence is lacking, the Panel recommends measuring serum AFP, hCG, and LDH before chemotherapy begins for those with mediastinal or retroperitoneal NSGCTs, to stratify risk and select treatment.

Evidence from subset analyses of retrospective series suggests that STM elevation is a statistically significant predictor of

treatment outcome for patients with extragonadal tumors. Standard risk stratification schemata incorporate STM assay results and help guide regimen choice.

I-3B. To predict response to or benefit from treatment?

Recommendation I-3B-1. The Panel recommends measuring AFP and hCG shortly before RPLND in patients with clinical stage I or II NSGCT. Those with rising concentrations are beyond stages IA or IB and should be treated with systemic therapy similar to the regimens used for patients with stage III disease.

Rising or persistent elevation of AFP or hCG concentration at RPLND is associated with an increased risk of relapse and decreased disease-specific survival, suggesting that the surgical procedure is less likely to cure patients with such indicators. They should be considered for chemotherapy.

Recommendation I-3B-2. Although conclusive evidence is lacking, the Panel recommends measuring hCG, AFP, and LDH immediately before chemotherapy for stage II or III testicular NSGCT. The magnitude of marker elevations guides choice of chemotherapy regimen and treatment duration.

As described in Recommendation I-3A-1, the magnitude of hCG, AFP, and LDH elevation predicts prognosis and secondary outcomes.

I-3C. To monitor treatment response or progression during or soon after therapy?

Recommendation I-3C. Although conclusive evidence is lacking, the Panel recommends measuring serum AFP and hCG at the start of each chemotherapy cycle and again when chemotherapy concludes. However, the Panel sees no indication to delay the start of chemotherapy until after the results of STM assays. Rising levels of AFP and/or hCG usually suggest progressive disease and the need to change regimen. Resect all residual disease for patients whose STM levels have normalized and who have resectable residual mass(es) after chemotherapy. Slow decline during treatment conveys higher risk of treatment failure but does not indicate a need to change therapy. Persistently elevated but slowly declining postchemotherapy levels do not indicate immediate need for additional chemotherapy; resection of residual masses need not be delayed until the markers normalize.

Patients whose marker levels do not decline from the start of cycle 1 to the start of cycle 2 should have repeat marker levels drawn during the second or third week of cycle 2 to determine whether the levels are rising—a finding that would change the treatment plan. The guideline recommends against using normalized AFP or hCG concentrations to select patients who might safely avoid postchemotherapy RPLND or residual tumor resection. Available evidence is insufficient to recommend changing therapy based solely on slow marker decline or selecting patients with NSGCT for intensified therapy based on an unsatisfactory rate of marker decline during initial cycles of standard-dose therapy. There is no evidence of benefit from

resecting residual tumor or from salvage surgery in patients with NSGCT and AFP or hCG concentrations that continue to rise during chemotherapy or soon after it concludes. Serial measurements must be obtained to determine whether levels are rising or falling.

I-4. Clinical question: In adult patients with NSGCT, are STM assays indicated after presumably definitive therapy for surveillance and routine monitoring to detect asymptomatic recurrence?

Recommendation I-4. Although conclusive evidence is lacking, the Panel recommends measuring AFP and hCG at each visit during surveillance after definitive therapy for NSGCT, regardless of stage. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every 1 to 2 months in the first year, every 2 to 4 months in the second year, every 3 to 6 months in the third and fourth years, every 6 months in the fifth year, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.

Increased serum concentration of AFP and/or hCG is a relatively low sensitivity marker for detecting relapses after presumably definitive therapy for NSGCT. Thus, measuring AFP and hCG alone is not a sufficient tool to monitor for relapse in these patients. However, rising markers are often the earliest evidence of relapse, and the false-positive rate is low. In addition, unlike radiographs and computed tomography scans, drawing blood for STMs does not expose the patient to the risks associated with radiation. Monitoring AFP and hCG levels thus permits earlier detection of relapse in many patients while exposing the patients to minimal risk. The cost effectiveness of monitoring tumor markers has not been thoroughly assessed.

Part II: Seminoma

II-3. Clinical question: In adult patients with pure seminoma undergoing treatment (or observation), are STM assays indicated for the following uses:

II-3A. To stage patients and predict prognosis before RPLND, radiation therapy, or chemotherapy?

Recommendation II-3A. Although conclusive evidence is lacking, the Panel recommends measuring postorchietomy serum concentrations of hCG and/or LDH for patients with testicular pure seminoma and measuring preorchietomy elevations. However, the Panel recommends against using postorchietomy serum concentrations of either hCG or LDH to stage or predict prognosis of patients with seminoma and involved nodes and/or metastatic disease.

The literature search found no evidence that demonstrated that there is clinical utility in measuring hCG and/or LDH after orchietomy for patients with testicular pure seminoma and preorchietomy elevations. Nevertheless, in the Panel's opinion, determining whether diagnostic orchietomy normalizes the STM elevations is informative and helps stage patients with no other seminoma signs or symptoms of seminoma that persist

after orchietomy. Persistently elevated or rising concentrations may indicate metastatic disease and warrant a thorough work-up. No patients with pure seminoma are classified as having poor prognosis, and neither hCG nor LDH concentrations affect their prognostic classification.

II-3B. To predict response to or benefit from therapy?

Recommendation II-3B. The Panel recommends against using tumor markers to guide treatment decisions for patients with seminoma. Evidence is lacking that selecting therapy based on tumor marker levels yields better outcomes. There are no studies that reported outcomes for patients with pure seminoma whose treatment was determined based on serum concentrations of hCG or LDH.

II-3C. To monitor treatment response or progression during or immediately after therapy?

Recommendation II-3C. The Panel recommends against using STMs to monitor response or progression of seminomas during treatment. However, hCG and AFP should be measured when seminoma treatment concludes. Rising concentrations usually indicate progressive disease and the need for salvage therapy (usually chemotherapy).

There are no reports on changes in STM concentration during chemotherapy among patients being treated for advanced seminoma or on the proportion of patients with pure seminoma who responded incompletely or briefly to primary therapy (radiation or chemotherapy) in whom progression was detected by rising marker concentrations versus other means of post-treatment evaluation. Roughly half of patients with seminoma who experience relapse after chemotherapy for metastatic disease have elevated hCG. Nevertheless, in the Panel's opinion, rising marker concentrations soon after therapy concludes usually signals progressive disease and the need to determine whether salvage chemotherapy is indicated. Patients who have been diagnosed with pure seminoma but who, in fact, have a mixed GCT may have elevated AFP at progression or relapse. Measuring AFP in these patients is of low diagnostic yield but may result in earlier diagnosis of relapse. The Panel did not endorse routine monitoring of LDH, because, unlike hCG and AFP, there is a high false-positive rate for LDH.

II-4. Clinical question: In adult patients with seminoma, are STM assays indicated after presumably definitive therapy for surveillance and routine monitoring to detect asymptomatic recurrence?

Recommendation II-4. Conclusive evidence is lacking for clinical utility of STMs in post-treatment surveillance for stage I seminoma, and the Panel recommends against this use. However, while direct evidence is lacking, rising tumor marker concentrations may be the earliest sign of relapse after therapy for advanced seminoma, and the Panel recommends measuring STMs at each visit for these patients. Since evidence also is lacking to directly compare outcomes for different monitoring intervals or durations, the Panel recommends using intervals within the range used in the available uncontrolled series: every

2 to 4 months in the first year, every 3 to 4 months in the second year, every 4 to 6 months in the third and fourth years, and annually thereafter. The Panel also recommends that surveillance should continue for at least 10 years after therapy is completed.

Evidence includes randomized controlled trials and uncontrolled series that reported monitoring STM concentrations during post-treatment follow-up. Imaging with computed tomography and/or x-ray was typically less frequent than STM assays but was included in each study. Therefore, STM monitoring alone is not recommended.

Patients who have been diagnosed with pure seminoma but who, in fact, have a mixed GCT may have an elevated AFP at relapse after chemotherapy for advanced disease; thus, the Panel recommends measuring AFP and hCG during surveillance. Measuring AFP in these patients is of low yield but may result occasionally in earlier diagnosis of relapse. Varying percentages of relapses were initially detected by STM elevations (5% to 40%).

Communication

Uses of STMs to inform treatment decisions for patients with GCTs is not a subject that is commonly understood by patients diagnosed with the disease, their families or caregivers, or the general public. The meaning of the term “serum tumor marker” is not self-evident to a layperson, and neither are the potential uses for results of these laboratory measurements. For these and other reasons, it is essential to educate patients about tumor markers using easily understood language and at a pace that enables them to absorb the information. The guideline suggests specific facts to convey to men with GCTs.

Methodology

The ASCO Expert Panel reviewed searches of MEDLINE and EMBASE and conducted a systematic review of the literature published between 1990 and the end of 2008. Panel members provided additional relevant references.

Additional Resources

JCO published an abridged version and ASCO published a full version of this guideline¹ on June 7, 2010. Both versions, as well as a slide set and other resources, are available at www.asco.org/guidelines/germcelltm. A guide for patients (“What to Know,”

which includes Questions to Ask Your Doctor) is available at www.cancer.net/whattoknow.

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