available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

MicroRNAs: Turning the Tide in Testicular Cancer

Nirmish Singla, John T. Lafin, Aditya Bagrodia *

Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Germ cell tumor (GCT)-associated microRNAs (miRNAs) are poised to radically change the way we care for patients with GCTs across all disease states, ushering in an era of personalized medicine from diagnosing testicular masses to managing patients with chemotherapy-refractory disease. These novel biomarkers hold the promise to improve on already excellent clinical outcomes by precisely individualizing treatment paradigms.

GCTs are unique in their ability to secrete measurable proteins (AFP, β-hCG, LDH) into the bloodstream and these comprise the conventional panel of serum tumor markers (STMs) for GCT. STMs are standard in diagnosing and monitoring patients with GCT, earning a separate S-stage designation in the TNM system [1]. The clinical utility of these markers is marred by poor sensitivity and specificity, as STMs are elevated in only 10–15% of seminomas, which never secrete AFP, and 60% of nonseminomas (NSGCT) [2]. Furthermore, STMs may be elevated nonspecifically by processes other than GCT and may be normal in the setting of radiographically and serologically occult metastatic disease. These limitations provide the impetus to identify novel biomarkers with superior performance characteristics compared to contemporary STMs.

miRNAs are small noncoding RNAs involved in epigenetic regulation of gene expression that have emerged as promising biomarkers for diagnosing and monitoring GCT. Several groups have identified a cluster of miRNAs that are not only expressed in testicular cancer tissue but are also secreted and measurable in the serum [3]. Among these clusters, miR-371a-3p has specifically exhibited greater accuracy than traditional STMs in GCT diagnosis. Impressively, it has been found that approximately 85% of seminomas secrete miR-371a-3p [4–7]—considerably higher than the 10–15% rate of conventional STM elevation seen in this cohort—and circulating miRNA levels appear to correlate with both clinical stage and tumor bulk [8,9], supporting a potential role in monitoring therapeutic response.

In the largest prospective study of miRNAs in GCT to date, Dieckmann et al. [10] recently examined the performance characteristics of serum miR-371a-3p in the diagnosis and monitoring of patients with testicular cancer. Across an impressive cohort of 616 patients with testicular cancer—including 359 seminomas and 257 NSGCTs—and 258 healthy males, they found that the miR-371a-3p test had 90% sensitivity, 94% specificity, 97% positive predictive value, 83% negative predictive value, and an area under the receiver operating characteristic curve of 0.966 for the primary diagnosis of GCT. Indeed, the miR-371a-3p test outperformed all of the classic STMs and even the combination of all three with respect to diagnostic accuracy. Notably, the majority (60%) of their patients had clinical stage I disease confined to the testicle, and among these patients, miR-371a-3p levels dropped after orchiectomy. Among the remaining patients who developed systemic disease, miR-371a-3p levels dropped after treatment with chemotherapy and were found to be elevated at relapse with 83% sensitivity and 96% specificity. Taken together, the results showed that miR-371a-3p levels correlated with clinical stage, primary tumor size, and response to treatment, supporting a clinical role for an miRNA-based test in GCT diagnosis and surveillance.

Although the miR-371a-3p test has not yet received regulatory approval for incorporation into clinical decision-making, the test conceivably has extensive and important applications across all disease states for patients with GCT. In those with clinical stage I disease (any T, N0M0S0), normal postorchiectomy STMs, and no radiographic evidence of metastases, anywhere from 10% to 50% of patients may harbor occult metastases. Our current ability to risk-stratify these patients is rudimentary at best, with lymphovascular invasion and the presence of embryonal

* Corresponding author. Department of Urology, University of Texas Southwestern Medical Center, 2001 Inwood Road, Dallas, TX 75390-9110, USA. Tel. +1 214 6458765.
E-mail address: aditya.bagrodia@utsouthwestern.edu (A. Bagrodia).

https://doi.org/10.1016/j.eururo.2019.06.010

carcinoma dictating risk in NSGCT patients and size/rete testis invasion stratifying seminoma patients. Patients with clinical stage I disease and elevated miR-371a-3p levels could be precisely identified and benefit from a single cycle of bleomycin, etoposide, and cisplatin chemotherapy, retroperitoneal lymph node dissection, or radiotherapy. Those destined to be cured by orchiectomy alone might be correctly identified by normal miR-371a-3p levels and hence spared the risks and morbidity of unnecessary intervention. Similarly, for patients with clinical stage IIA disease, the 20% with benign pathology can be accurately identified and spared treatment. Thus, there may be a role for miR-371a-3p in informing treatment strategies for patients with early-stage disease. At the other end of the spectrum, for patients receiving chemotherapy, miR-371a-3p may help in assessing response to therapy, while for patients with residual masses after chemotherapy, the test may help in determining the utility of salvage surgery.

An important caveat of the test is that pure teratoma, a classically chemoresistant tumor, does not exhibit elevated miR-371a-3p levels. Hence the ability to discriminate between benign processes and teratoma is limited using this test. Although recent data from The Cancer Genome Atlas research network suggest that teratomatous elements express miR-375 in tissue [11], this has not been validated in serum samples, and there remains a considerable need to identify a reliable biomarker for teratoma. Despite this limitation, miR-371a-3p could supplant the need for traditional surveillance imaging in all patients with seminoma, where teratoma is an exceedingly rare occurrence. miR-371a-3p could limit the number of axial scans required for NSGCT monitoring, for which teratoma and the rare instances of growing teratoma syndrome and malignant transformation must also be considered. This could dramatically reduce costs and radiation exposure for this young population.

Further validation of the utility of miR-371a-3p in two large clinical trials that are accruing (AGCT1531; NCT03067181) and expected to open soon (SWOG-S1823) will provide further insight into whether the test can be implemented in the routine clinical management of patients with GCT. Comparison of the performance characteristics of this test against the current gold standard (conventional STMs and imaging) is imperative, and methods for collecting and processing blood samples must also be standardized for widespread use of the miRNA test. Undoubtedly, the evidence in support of miR-371a-3p as a promising biomarker for GCT continues to mount. Ultimately, miRNAs may be the key to turning the tide in personalizing the care for testicular cancer patients.

Conflicts of interest: The authors have nothing to disclose.

References

[1] American Joint Committee for Cancer. Collaborative stage for TNM. 7th edition. American Joint Committee for Cancer; 2010.
[2] Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol 2010;7:610–7.
[3] Murray MJ, Halsall DJ, Hook CE, Williams DM, Nicholson JC, Coleman N. Identification of microRNAs from the miR-371∼373 and miR-302 clusters as potential serum biomarkers of malignant germ cell tumors. Am J Clin Pathol 2011;135:119–25.
[4] Belge G, Dieckmann KP, Spiekermann M, Balks T, Bullerdiek J. Serum levels of microRNAs miR-371-3: a novel class of serum biomarkers for testicular germ cell tumors? Eur Urol 2012;61:1068–9.
[5] Syring I, Bartels J, Holdenrieder S, Kristiansen G, Muller SC, Ellinger J. Circulating serum miRNA (miR-367-3p, miR-371a-3p, miR-372-3p and miR-373-3p) as biomarkers in patients with testicular germ cell cancer. J Urol 2015;193:331–7.
[6] van Agthoven T, Looijenga LHJ. Accurate primary germ cell cancer diagnosis using serum based microRNA detection (ampTSmiR test). Oncotarget 2017;8:58037–49.
[7] Bezan A, Gerger A, Pichler M. MicroRNAs in testicular cancer: implications for pathogenesis, diagnosis, prognosis and therapy. Anticancer Res 2014;34:2709–13.
[8] van Agthoven T, Eijkenboom WMH, Looijenga LHJ. microRNA-371a-3p as informative biomarker for the follow-up of testicular germ cell cancer patients. Cell Oncol 2017;40:379–88.
[9] Radtke A, Hennig F, Ikogho R, et al. The novel biomarker of germ cell tumours, micro-RNA-371a-3p, has a very rapid decay in patients with clinical stage 1. Urol Int 2018;100:470–5.
[10] Dieckmann KP, Radtke A, Geczi L, et al. Serum levels of microRNA-371a-3p (M371 test) as a new biomarker of testicular germ cell tumors: results of a prospective multicentric study. J Clin Oncol 2019;37:1412–23.
[11] Shen H, Shih J, Hollern DP, et al. Integrated molecular characterization of testicular germ cell tumors. Cell Rep 2018;23:3392–406.